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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

National Institute of Mental Health

PROJECT NUMBER

Z01 MH 02188-03 OCD

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Biological Studies of Borderline Personality Disorder

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | D.L. Gardner | Staff Psychiatrist | OCD, NIMH |
| Others: | R.W. Cowdry | Clinical Director | NIMH |
| | K.M. O'Leary | Social Worker (Research) | OCD, DIRP, NIMH |
| | D. Pickar | Chief, Sec. on Clinical Studies | NS, NIMH |
| | P. Lucas | Clinical Fellow, NRSA Fellow | NS, NIMH |
| | D.L. Murphy | Chief | LCS, NIMH |

COOPERATING UNITS *(if any)*

Office of the Director, Division of Intramural Research Programs, NIMH; Biological Psychiatry Branch, NIMH; Laboratory of Clinical Science, NIMH

LAB/BRANCH

Office of the Clinical Director

SECTION

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1.7 | 1.5 | 0.2 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

0.6
5:571
76
2
1

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

## NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00183-02 BP

PERIOD COVERED

October 1, 1986 - September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Biology and behavior of aggression and suicide

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Gerald L. Brown, M.D.,Medical Officer, BPB, NIMH

F.K. Goodwin, M.D., Director, IRP, NIMH; R.M. Post, M.D.,Chief, BPB, NIMH; M. Linnoila, M.D., Chief, LCS, NIAAA; J. Kleinman, M.D., St. Elizabeth's Hospital, NIMH; D.L. Murphy, M.D., Chief, LCS, NIMH; J.L. Rapoport, M.D., Chief, CHP, NIMH

COOPERATING UNITS *(if any)*

BPB, CHP, LCS, OD, NIMH; St. Elizabeth's Hospital; LCS, NIAAA, National Naval Medical Center

LAB/BRANCH

Biological Psychiatry Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 2.0 | 1.6 | .4 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

For several years, studies that relate human aggression (including hyperactivity and conduct disorder in children) and suicide to various behavioral and biological factors have been ongoing. Some of the most significant findings have included pharmacokinetic and metabolic studies of amphetamine administered to hyperactive and conduct disordered children, and a trivariate relationship among a history of aggressive behavior, a history of suicidal behavior, and lower cerebrospinal fluid (CSF) 5-hydroxyindoleacetic acid (5HIAA). More recently, data indicate that certain aggressive, impulsive, and depressive characteristics in childhood are also inversely related to CSF 5HIAA measured during late adolescence; family instability during childhood also appears to be associated with increased likelihood of aggressive and/or suicidal behavior in late adolescence. These data, along with the work of other investigators studying aggressive behavior in childhood, indicate the possibility of traits associated with disordered serotonin metabolism; further, the less consistent relationship between lower CSF 5HIAA and suicidal behaviors vs. aggressive behaviors, may indicate that some suicidal behaviors are a self-destructive manifestation of a more basic destructive (aggressive/impulsive) trait.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

## NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 MH 00070-14 BP

PERIOD COVERED
October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Psychological and Biological Interactions in the Mood and Anxiety Disorders

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | |
|---|---|---|
| Robert M. Post, M.D. | Chief | BP NIMH |
| Dr. T. Colburn | Research Services Branch, NIMH | |
| Dr. R. Cohen | Laboratory of Cerebral Metabolism, NIMH | |
| Dr. L. DeLisi | Clinical Neurogenetics Branch, NIMH | |
| Dr. T.W. Uhde | Biological Psychiatry Branch, NIMH | |

COOPERATING UNITS *(if any)*
BPB,CNG,NSB,NPB,CPB,LCM,LCS,LPP,RSB,IRP, NIMH; DEB, NICHD; IRP, NIAAA; PDS, NIH; USUHS, Dept of Def.; U. of CA; Tufts U.; U. So. Carolina Med. Sch.; INSERM: St. Elizabeth's Hospital; St. Michael's Hospital

LAB/BRANCH
Biological Psychiatry Branch

SECTION
Section on Psychobiology

INSTITUTE AND LOCATION
NIMH, NIH, Bethesda, Maryland 20205

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 13.0 | 7.0 | 6.0 |

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Evaluation, study, and treatment of patients with manic-depressive and schizoaffective illness are the primary goals of the Section. Double-blind, placebo-controlled clinical trials are employed to evaluate routinely used and novel agents for the treatment of these disorders. Anticonvulsants such as carbamazepine have been demonstrated to be clinically effective in the acute and prophylactic treatment of manic-depressive illness. We have identified possible clinical and biochemical markers of response to lithium versus carbamazepine and other agents. For example, antimanic responders to carbamazepine appear to be more severely ill, more dysphoric, and more rapidly cycling than non-responders, i.e., variables that tend to be associated with lithium nonresponse. In attempting to elucidate possible mechanisms of action, we have found that alpha-2 noradrenergic and "peripheral-type" benzodiazepine receptor mechanisms may be important to the anticonvulsant if not the psychotropic effects of carbamazepine. Other neurotransmitter, modulator, and peptide substances are being studied which may account for carbamazepine's positive effects on mood and behavior. The Section also seeks to identify regional alterations in brain electrophysiological and metabolic activity that are related to changes in behavior and cognition in affective illness. A clinical probe of limbic system excitability utilizing a novel provocative agent, procaine, is also being employed. Procaine selectively increases fast activity over the temporal lobe in association with a variety of behavioral and cognitive alterations and secretion of cortisol, ACTH, and prolactin. Animal models of electrophysiological and pharmacological kindling and cocaine-induced behavioral sensitization are studied and implicate conditioning and learning processes in the progressive behavioral changes induced. These models may help provide new clinical and biochemical insights into the mechanisms that underlie the progressive and long-term changes in behavior in a variety of clinical syndromes including cocaine-induced psychopathology and affective illness.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00071-07 BP

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Psychobiological Correlates and Treatment of Panic and Related Mood Disorders

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

T.W. Uhde, M.D., Chief, Unit on Anxiety and Affective Disorders, BPB, NIMH

| | |
|---|---|
| R.M. Post, M.D. | BPB, NIMH |
| J.-P. Boulenger, M.D. | French National Institute for Health and Medical Research, Cannes, France |
| P.P. Roy-Byrne, M.D. | Univ. of Washington, Seattle, Washington |
| B.J. Vittone, M.D. | BPB, NIMH |
| B. Scupi, M.S.W. | BPB, NIMH |

COOPERATING UNITS *(if any)* CNB, CRB, LCS, LPP, NSB, OD, NIMH; Outpatient Dept., NIMH; LCS, NIAAA; French Nat'l Inst. of Hlth. & Med. Res., Cannes; UC, Irvine & San Diego; VA Med. Ctr., Bronx; Med. Univ. of So. Carolina, Charleston; Univ. Pittsburgh, Pittsburgh, Univ. of Washington, Seattle; Catholic Univ., Washington, D.C.

LAB/BRANCH

Biological Psychiatry Branch

SECTION

Unit on Anxiety and Affective Disorders

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 5 | 4 | 1 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Patients with pathological degrees of anxiety who meet DSM III-R criteria for panic disorder, with or without agoraphobia; generalized anxiety disorder; or social phobia are evaluated using psychological, physiological, and biochemical methodologies. Patients with major affective illness, particularly those with a significant anxiety component, are also eligible for participation in the program. Particular attention is given to the role of the noradrenergic, dopaminergic, adrenergic, and serotonergic neurotransmitter systems as assessed by: 1) measurement of the metabolites MHPG and HVA in plasma; 2) adrenergic receptor number and function in platelets; and 3) neuroendocrine and behavioral responses to the alpha-2 adrenergic agonist clonidine and antagonist yohimbine and the serotonin agonist m-chlorophenylpiperazine (MCPP). Research investigating the relationship of noradrenergic and adenosinergic function to other neurotransmitter systems and the hypothalamic-pituitary-adrenal axis also has been initiated. Caffeine and nifedipine challenges are administered to assess their behavioral and biochemical effects. Other approaches to understanding the pathophysiology of anxiety and its potential treatment with alprazolam, carbamazepine, clonidine, imipramine and verapamil will be explored.

An animal model using genetically "nervous" and "normal" pointer dogs has been developed and studied in relation to noradrenergic and adenosinergic function.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00452-12 BP

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Neuroendocrine Studies of Major Psychiatric Disorders

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Philip W. Gold, M.D., Chief, Section on Clinical Neuroendocrinology, BPB, NIMH

Dr. D.L. Loriaux, Chief, Developmental Endocrinology Branch, NICHD
Dr. E.H. Oldfield, Senior Investigator, Surgical Neurology Branch, NINCDS
Dr. G.P. Chrousos, Senior Investigator, Developmental Endocrinology Branch, NICHD
Dr. R.M. Post, Chief, Biological Psychiatry Branch, NIMH
Dr. D.R. Rubinow, Chief, Unit on Peptide Studies, BPB, NIMH

COOPERATING UNITS *(if any)*

BPB, CNB, LCS, LNP, NIMH: DEB, EB, NICHD; SNB, NINCDS; SOB, NCI; LCS, NIAAA; UCLA School of Medicine; University of Pittsburgh School of Medicine

LAB/BRANCH

Biological Psychiatry Branch

SECTION

Section on Clinical Neuroendocrinology

INSTITUTE AND LOCATION

NIMH, Bethesda, MD 20892

| | | |
|---|---|---|
| TOTAL MAN-YEARS: 11.0 | PROFESSIONAL: 12.0 | OTHER: 4.0 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

A primary focus of our work has been on mechanisms of physical and emotional stress and their relevance to major psychiatric and endocrine disorders. Our recent work with corticotropin releasing hormone (CRH) illustrates our comprehensive approach to this area of inquiry. For instance, we have advanced data which indicate that CRH is of physiological relevance to human pituitary-adrenal adrenal function, demonstrated its role in the pathophysiology of hypercortisolism in depression and anorexia nervosa, and administered it as a clinically useful means of determining the differential diagnosis between depression and Cushing's disease. Our data regarding interactions between the CRH system and the locus ceruleus-norepinephrine system suggest that a positive feedback loop between these two major effectors of the stress response may account for many of the clinical and biochemical manifestations of melancholic depression. As indirect support for a role of CRH in the mood component of depression, we have shown that procaine produces does-dependent activation of pituitary-adrenal function in association with mood changes in patients with affective illness. Moreover, in vitro studies show procaine-induced dose-dependent activation of the CRH neuron which is prevented by carbamazepine. In clinical studies with volunteers and patients with panic disorder, we have implicated CRH in exercise and lactate-induced panic and have advanced in vivo and in vitro data that alprazolam may exert therapeutic effects by suppressing the CRH neuron. In studies exploring the mechanisms by which the immune system may stimulate adrenal corticosteroid counterregulation of the immune response, we have shown that both interleukin-I and interleukin-II produce dose-dependent activation of the CRH neuron.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01090-11 BP

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Studies of Central Nervous System Functional Anatomy

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Miles Herkenham, Ph.D., Chief, Unit on Functional Neuroanatomy, SCN, BPB, NIMH

Stafford McLean, Senior Staff Fellow, BPB, NIMH
Linda S. Brady, Staff Fellow, BPB, NIMH
John B. Glowa, Research Psychologist, BPB, NIMH
Richard B. Rothman, Guest Worker, LP-DSMHR, NIMH
Kenner C. Rice, Chemist, LN, NIDDK

COOPERATING UNITS *(if any)*

Neuroscience Branch, Laboratory of Pre-Clinical Pharmacology, SEH, NIMH

LAB/BRANCH

Biological Psychiatry Branch

SECTION

Clinical Neuroendocrinology, Unit on Functional Neuroanatomy

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 5.2 | 5.2 | |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

A sensitive method for light microscopic localization of brain receptors by in vitro autoradiography was developed previously in this laboratory. By this method we have mapped the locations of drug and neurotransmitter receptors in the brains of rats and other vertebrates, including primates. Immunohistochemistry is used to compare the locations of transmitter-specific pathways with the locations of the relevant receptors. The non-correspondence, or "mismatch" between the locations of receptors and transmitters in the opiate and tachykinin systems, as well as others, allows hypotheses about parasynaptic circuitry in the central nervous system. Physiological activation of vasopressin dynorphin pathways in the posterior pituitary altered kappa opiate receptor binding in the neurohypophysis, a site of parasynaptic communication. Current and planned work uses similar strategies to better understand the forms of functional intercellular communication.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00180-05 BP

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Psychobiology and Treatment of Menstrually-Related Mood Disorders

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

David R. Rubinow, M.D., Chief, Unit on Peptide Studies, BPB, NIMH

P. Schmidt, BPB, NIMH; M.C. Hoban, BPB, NIMH; K. Denicoff, BPB, NIMH; G. Merriam, ERRB, NICHD; R. Elin, CPD, CC, NIH; H. Weingartner, BPB, NIMH; B. Both-Ortmann, BPB, NIMH; F. Putnam, St. Elizabeth's Hospital; D. Raben, ERRB, NICHD; N. Hall, George Washington University; E. Bou, CC, NIH; N. Rosenthal, CPB, NIMH; R. Anderson,

COOPERATING UNITS *(if any)*

BPB, CPB, NIMH; ERRB, NICHD; HEB, NHLBI; CPD, CC, NIH; St. Elizabeth's Hospital; George Washington University

LAB/BRANCH

Biological Psychiatry Branch

SECTION

Unit on Peptide Studies

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 2 | 1 | 1 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The occurrence of dramatic changes in mood, behavior, cognition and somatic functioning in some women in relation to the menstrual cycle has recently been the focus of a great deal of public scrutiny. This project is designed to study the psychobiology and treatment response of women with well-defined menstrually-related mood disorders. The longitudinal screening methods developed by this group are capable of distinguishing women with menstrually-related mood syndromes from those who only believe that they have such a syndrome. With these methods, we have identified the following: 1) menstrual cycle phase dependent changes in perception and cognitive performance in patients with menstrually-related mood disorders but not controls; 2) an increased tendency to dissociate in patients versus controls; 3) an increased prevalence of abnormal basal and stimulated thyroid measures in patients; 4) a higher than expected frequency of hypoglycemic episodes following glucose tolerance testing in women with premenstrual syndrome irrespective of menstrual cycle phase; and 5) preliminary evidence of the efficacy of alprazolam in the treatment of premenstrual syndrome relative to placebo or other treatments employed. The goals of this project are to detect and accurately describe menstrually-related mood disorders, explore their pathophysiology and response to pharmacological and environmental manipulation, and to document the relationship between reproductive endocrine change and disorders of mood as a way of further investigating the neurobiology of psychiatric illness.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00181-04 BP

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Hormonal Studies of Affective Disorder

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

David R. Rubinow, M.D., Chief, Unit on Peptide Studies, BPB, NIMH

P. Sunderland, M.D., LCS, NIMH; M. Linnoila, M.D., LCS, NIAAA; M.; S. Bracha, M.D., M, SMRC; S.R.B. Weiss, Ph.D., BPB, NIMH; W. Kaye, M.D., Univ. of Pittsburgh; J. Crawley, Ph.D., NSB, NIMH; K. Denicoff, M.D., BPB, NIMH; P. Hauser, M.D., BPB, NIMH; J. Hill, Ph.D., NSB, NIMH

COOPERATING UNITS *(if any)*

BPB, LCS, NSB, NIMH; LCS, NIAAA; NCI; M, SMRC; SUNY, New York; University of Pittsburgh

LAB/BRANCH

Biological Psychiatry Branch

SECTION

Unit on Peptide Studies

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 2 | 1 | 1 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Studies of somatostatin and cortisol in relation to affective and other neuropsychiatric disorders have continued. Additionally, further studies of the mechanisms of interleukin-2-induced neurotoxicity have been performed in rodents.

A) Somatostatin - CSF somatostatin has been measured in an expanded group of neuropsychiatric patients including patients with multiple sclerosis and neurological controls, patients with alcoholism, pathological gambling, and Huntington's dementia. Significant correlations were observed between somatostatin and performance on the Wechsler Memory Scale, supporting our earlier observations (and perhaps the clinical relevance) of decreased somatostatin levels in patients with neuropsychiatric disorders characterized by cognitive impairment. Studies of the regional concentrations of brain somatostatin in post-mortem schizophrenics, suicide victims, and accident victims have been completed with the sample code not yet broken.

B) Cortisol - A salivary cortisol method, developed and validated in our laboratory, has been used to longitudinally follow patients with affective and anxiety disorders. This method shows great promise for studies of ambulatory patients with affective disorder.

B) Interleukin-2 - No changes in blood-brain-barrier permeability were observed in rats treated with interleukin-2, irrespective of the size of the tracer employed. These findings contradict previous reports and leave unresolved the mechanism of lymphokine-induced neurotoxicity.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

# NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00182-04 BP

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Behavioral Medicine

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

David R. Rubinow, M.D., Chief, Unit on Peptide Studies, BPB, NIMH

Dr. Kirk Denicoff, Biological Psychiatry Branch, NIMH
Dr. David Pickar, Clinical Neuroscience Branch, NIMH
Dr. Steven Rosenberg, Surgery Branch, NCI
Dr. Pim Brouwers, Georgetown University, Washington, D.C.
Dr. Clifford Lane, Laboratory of Immunoregulation, NIAID

COOPERATING UNITS *(if any)*

BPB, NSB, LPP, CPB, NIMH; SB, PB, FCRF, NCI; LIR, LCI, NIAID; CCM, CC; OD, CE, A&R, NIADDKD; MD, CB, NHLBI; St. Michael's Hosp., Toronto; Georgetown Univ.

LAB/BRANCH

Biological Psychiatry Branch

SECTION

Unit on Peptide Studies

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 2 | 1 | 1 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Eight protocols are currently active and conducted out of the Consultation-Liaison Service-based behavioral medicine research program. These protocols examine the phenomenology and biological correlates of illness or treatment-induced mood, behavioral, and cognitive changes. The protocols address such areas as: a) the effects of previous psychiatric history on the psychiatric morbidity associated with certain diseases and their treatment; b) the psychiatric phenomenology of certain diseases and their treatment; c) the treatment response characteristics of psychiatric disorders associated with diseases or their treatment; d) biochemical factors that may serve as predictive diagnostic markers for illness or for treatment-associated mood/behavioral or cognitive syndromes; e) the effects of mood state alterations on immunologic function. Significant findings to date include demonstration of the following: 1) significant neuropsychological cognitive impairment in patients with AIDS compared with seropositive patients, chronically medically ill patients, or controls; 2) significant cognitive and affective deterioration following removal of thyroid hormone replacement, with no differential effects of $T_4$ and $T_3$ on mood and cognition; 3) absence of evidence of acute immune changes following hypnotically-induced affective states; 4) a significant effect of dose on interleukin-2-induced neuropsychiatric toxicity; 5) preliminary confirmation of alpha-delta intrusion in patients with fibromyalgia; 6) preliminary evidence of exaggerated response to novelty in patients with chest pain and normal coronary arteries.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00147-12 BP

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Behavioral and Physiological Effects of Brain Peptides and Other Psychoactive Compounds

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Agu Pert, Ph.D., Chief, Unit on Behavioral Pharmacology, BPB, NIMH;
Lorna Estal, Visiting Fellow, BPB, NIMH; R.J. Weber, Sr. Staff Fellow, SNB, NINCDS; K.C. Rice, LC, NIADDK; B. DeCosta, Visiting Fellow, LC, NIDDKD; A.A. Hagen, American U.; T. Seeger, Pfizer Central Research, Groton, Ct.; H.D. Everist, Guest Worker, BPB, NIMH; C.C. Chiueh, Staff Fellow, LCM, NIMH; S.R.B. Weiss, Staff Fellow, BPB, NIMH; C.B. Pert, CNB, NIMH; P. Glue, LCS, NIAAA; D. Nutt, LCS, NIAAA

COOPERATING UNITS *(if any)*

BPB, CNB, LCM, NIMH; LC, NIADDK; LC, NIDDKD; LCS, NIAAA; SNB, NINCDS; Pfizer Central Research, Groton, Ct., American University, Washington, D.C.

LAB/BRANCH

Biological Psychiatry Branch

SECTION

Unit on Behavioral Pharmacology

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 2.5 | 1.5 | 1 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Phencyclidine produces behavioral excitation through a dopamine independent mechanism in the nucleus accumbens, probably by blocking the excitatory amino acid NMDA receptor. Motor asymmetries produced by phencyclidine are caused by activation of pathways projecting caudally from the substantia nigra. Opiate-induced suppression of immune function appears to be mediated, at least in part, through the periaqueductal gray matter. The periaqueductal gray matter in general seems to be an important region of the brain for regulating the immune function. Nicotine produces behavioral excitation by activating nigrostriatal and mesolimbic dopamine pathways. Locomotor activation produced by amphetamine and cocaine in the nucleus accumbens is mediated through activation of a variety of efferent pathways projecting to the striatal fundus, ventral pallidum, zona reticulata, and the medial and lateral olivary complex. Kappa opiate receptors modulate locomotor behaviors as well as a variety of homeostatic mechanisms. The depressant actions of kappa opiate agonists are not produced through the opiate receptor but appear to be nonspecific.

| DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE<br>**NOTICE OF INTRAMURAL RESEARCH PROJECT** | PROJECT NUMBER<br>Z01 MH 00400-05 BP |
|---|---|

PERIOD COVERED
October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Protein Phosphorylation in Brain

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*
Jitendra Patel, Visiting Associate, Unit on Neurochemistry, BPB, NIMH

Sheela Vyas, BPB, NIMH; Anne-Marie O'Carroll, LCS, NIMH; Douglas Kligman, LCB, NIMH; Savella Detera, CNB, NIMH; Peter Fishman, DMNB, NINCDS; John Bishop, ET, NINCDS

COOPERATING UNITS *(if any)*
CNB, LCS, LCB, NIMH; DMNB, ET, NINCDS

LAB/BRANCH
Biological Psychiatry Branch

SECTION
Unit on Neurochemistry

INSTITUTE AND LOCATION
NIMH, NIH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1.4 | 1.2 | 0.2 |

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

We have extended our characterization of the major protein kinase C substrates of 87,000 dalton (Mr 87). We have purified this phosphoprotein to homogeneity. Purified Mr 87 was used to elucidate its amino acid composition, site of phosphorylation and partial amino acid sequence. Polyclonal antibodies to Mr 87 were raised and were used to perform immuno-localization of this phosphoprotein. Cloning of Mr 87 and other studies attempting to elucidate the function of MR 87 are in progress.

Our previous work had demonstrated that protein kinase C is involved in the regulation of receptor activity and neurotransmitter release. This work was further extended.

Further characterization and isolation of the 94,000 dalton cyclic AMP-dependent protein kinase substrate was performed.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01831-11 BP

PERIOD COVERED

October 1, 1986 - September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Basic and Clinical Studies of Neuronal and Glial Enolases

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Paul J. Marangos, Ph.D. Chief, Unit on Neurochemistry, BPB, NIMH

| | |
|---|---|
| J.M. Polak | Chairperson, Histochemistry Dept., Royal Medical School, London |
| A.G. Pearse | Professor Emeritus, Royal Medical School, London |
| D. Schmechel | Assoc. Professor, Neurology, Duke University |
| E. Ginns | Neurologist, NSB, NIMH |
| B. Martin | Biochemist, NSB, NIMH |
| D. Van Lubitz | Physiologist, Georgetown Univ. Medical School |

COOPERATING UNITS *(if any)*

Royal Med. School, London; Hoffmann La Roche; Duke U.; Vanderbilt U.; U. of Texas; U. of Virginia; UCLA Med. School; U. of Ulm, Germany; Georgetown Med. School; NSB, NIMH; Children's Hosp., Phila.; Johns Hopkins U.; Finsen Inst., Copenhagen.

LAB/BRANCH

Biological Psychiatry Branch

SECTION

Unit on Neurochemistry

INSTITUTE AND LOCATION

NIMH, ADAMHA, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1.4 | 0.5 | 0.9 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The basic neurobiology and potential clinical utilization of neuron specific enolase (NSE) has been a long-standing interest in our laboratory. During the past year, studies have begun to focus on the molecular biology of NSE in an effort to use the brain enolase isoenzyme system as a model to study neuron specific gene expression. We now have cDNA probes for both NSE and non-neuronal enolase (NNE). The probes have been characterized and in situ hybridization studies have been performed in human brain. Our cDNA probe for NSE only labels neurons whereas the probe for NNE preferentially labels glial cells. Studies performed using northern blots in both rat and guinea pig brain reveal that the mRNA for NSE is substantially larger than that for NNE. There is approximately a 75% homology within the coding region for human NNE and NSE (some 1700 base pairs). The 3'non-coding region is much larger for NSE and has very little homology to that of NNE, a fact we made use of to generate specific probes. Studies are in progress regarding the NNE to NSE switch that occurs during neural differentiation.

Studies are also in progress to determine the effect of cerebral ischemia on brain NSE levels in gerbil brain. In these studies we will attempt to demonstrate that NSE levels can be used as an index of neural damage post ischemia. The effect of various protective agents such as adenosine receptor agonists will also be assessed. Clinical studies assessing NSE levels in both human CSF and serum consequent to stroke are also in progress. The goal here is to determine whether NSE levels are correlated with the degree of post-ischemic neurologic damage.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01833-07 BP

PERIOD COVERED

October 1, 1986 - September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Adenosine Receptors in the CNS

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

| | | |
|---|---|---|
| Paul J. Marangos, Ph.D. | Chief, Unit on Neurochemistry, | BPB, NIMH |
| J. Patel | Biochemist, | BPB NIMH |
| R. M. Post | Chief | BPB NIMH |
| S. Cohen | Neurologist | Georgetown Univ. |
| Dag Von Lubitz | Neurologist | Georgetown Univ. |
| N. Sperekalis | Chairman, Dept. of Physiology | Univ. Cincinnati |
| K. Jacobsen | Staff Fellow | LBC, NIADD |

COOPERATING UNITS (if any)

BPB, CNB, NIMH; LBC, NIADD; CP, NCI; U. of Cincinnati, Georgetown Univ.

LAB/BRANCH

Biological Psychiatry Branch

SECTION

Unit on Neurochemistry

INSTITUTE AND LOCATION

NIMH, ADAMHA, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1.7 | 0.6 | 1.1 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The pre-clinical evaluation of both adenosine receptor and adenosine uptake site continue to occupy a major portion of the Unit's resources. We have described the complete anatomical distribution of the adenosine uptake site using $[^3H]$dipyridamole autoradiography and shown by these binding experiments that there are multiple populations of brain adenosine uptake sites. Studies measuring adenosine uptake in synaptoneurosomes support the binding and autoradiography. More evidence has been gathered indicating that carbamazepine is acting as an adenosine antagonist. Xanthine-induced seizures have been studied using the new $A_1$-specific antagonist, XAC. Evidence was generated showing that XAC-induced seizures differ from those induced by caffeine in that they are not blocked by RO-15-1788, a benzodiazepine receptor blocker. We have also shown increased adenosine uptake sites in drug resistant human breast cancer cell cultures, suggesting that the adenosine uptake site may be involved in the phenomenon of multi-drug resistance.

Recent studies have focused on the role of adenosine agonists as protective agents during cerebral ischemia. The post-ischemic neuropathy is being characterized as it relates to adenosine, glutamate, and benzodiazepine status at both the binding and autoradiographic level. These studies will hopefully assess the potential utility of adenosine agonists in the treatment of stroke patients.

| | |
|---|---|
| DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE<br>NOTICE OF INTRAMURAL RESEARCH PROJECT | PROJECT NUMBER<br>Z01 MH 02193-05 CP |

PERIOD COVERED
October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Clinical Studies of Insomnia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Pnncipal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: W. B. Mendelson Chief, Section on Sleep Studies CPB/NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH
Clinical Psychobiology Branch

SECTION
Section on Sleep Studies

INSTITUTE AND LOCATION
NIMH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1.5 | 0.3 | 1.2 |

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Our work has shown insomniacs have some disturbance of perception. We have reported insomniacs have cognitive difficulties during the day. Their sleep is not different when compared to normals, but insomniacs report only half as much sleep as their normal controls. This suggests insomniacs have some misperception of their state of consciousness.

In an earlier study, we used meaningful (subject's name) and meaningless(electronic tone) stimuli to arouse the subject from different stages of sleep(just after lights out, stage II, stage IV, REM, after a movement time). Subjects were most difficult to arouse from REM and stage IV. The subjects were insomniacs and their matched controls.

In our current study, we are interested in the effects of hypnotics on this paradigm. Although the effects of hypnotic on subjective and objective measures of sleep is well documented for continuous sleep, little is known about their effects on sleep with forced awakenings. We found the hypnotic, flurazepam, raised the arousal threshold for all stages of sleep, but did not alter subjective measures of sleep when compared to placebo.

This project is no longer being pursued by the Branch and was terminated in March, 1987.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02197-01 CP

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Study of the Effects of Light and Triazolam on Delayed Sleep Phase Syndrome

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | N. Rosenthal, | Chief, Outpatient Services | CPB/NIMH |
| Others: | K. Kelly | Medical Staff Fellow | CPB/NIMH |
| | J. Vanderpool | Medical Staff Fellow | CPB/NIMH |
| | P. Schulz | Social Worker | CPB/NIMH |
| | T. Wehr | Chief, Clinical Psychobiology Branch | CPB/NIMH |
| | E. Souetre | Visiting Fellow | CPB/NIMH |

COOPERATING UNITS *(if any)*

Richard Allen, Ph.D., Johns Hopkins Sleep Center, Upjohn Pharmaceutical Company

LAB/BRANCH

Clinical Psychobiology Branch

SECTION

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 2.5 | 0.5 | 2.0 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Delayed sleep phase syndrome (DSPS) is a condition characterized by a delay in the timing of sleep onset and waking. Generally present from an early age, DSPS usually produces considerable difficulties for those who are required to function on a 9-to-5 schedule. Most subjects have tried unsuccessfully to correct their sleep-wake cycle many times. One type of currently available treatment, chronotherapy, involves delaying the timing of sleep onset further each day until it reaches the desired clock time. Although this is quite effective in some cases, it is inconvenient and the benefits are often transient.

The object of the present study is to recruit subjects who complain of DSPS, to determine the clinical and demographic characteristics of these individuals, and to try to correct their circadian rhythm abnormalities by judicious use of exposure to bright light and darkness, and by using the short-acting benzodiazepine, triazolam. Both of these strategies are derived from studies of circadian rhythms in animals, the timing of which is ordinarily influenced by the light-dark cycle. In recent years we have found that light of intensity greater than ordinary indoor lighting has a variety of effects on brain function. For example, it is capable of suppressing melatonin, reversing depression in seasonal affective disorder, altering norepinephrine and serotonin metabolism, and affecting resting metabolic rate and immune function. There is also evidence that bright light can influence the timing of circadian rhythms in humans.

We identified 93 subjects with DSPS and noted their reported patterns of sleeping and waking, as well as the difficulties encountered as a result of their sleep problem. We have studied sleep architecture in 11 cases and have not found patients to be suffering from another type of sleep disturbance. Three patients have been treated with both active (bright light in the morning plus dark goggles in the evening) and control (dimmer light in the morning and transparent goggles in the evening) light treatment conditions, and it appears that the active but not the control condition has a beneficial effect on the timing of sleeping and waking. However, the results are preliminary and more subjects will have to be run before a definitive statement can be made as to the value of bright light in the treatment of DSPS. We have yet to explore the value of triazolam in this condition.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02201-05 CP

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Early Versus Late Partial Sleep Deprivation in the Treatment of Depression

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | D. Sack | Chief, Inpatient Services | CPB/NIMH |
| Others: | T. Wehr | Chief, Clinical Psychobiology Branch | CPB/NIMH |
| | N. Rosenthal | Chief, Outpatient Services | CPB/NIMH |
| | W. Mendelson | Chief, Unit on Sleep Studies | CPB/NIMH |

COOPERATING UNITS *(if any)*

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Clinical Psychobiology Branch

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NIMH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| | | |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Total sleep deprivation, partial sleep deprivation, and shifting the time of the sleep period several hours earlier than usual can improve depression and can induce mania. Also, recovery sleep after these interventions can induce depression. Thus, changes in the timing and duration of sleep could trigger episodes of depression and mania during the natural course of affective illness, and manipulations of sleep could be used to treat and to prevent affective episodes. This project was designed to investigate the importance of the timing of sleep in patients' clinical responses to sleep manipulations. In particular, we hypothesized, on the basis of previous findings, that being awake or asleep in the second half of the night was critical for the responses. Identification of a critical circadian phase for these effects of sleep would provide an important clue to their mechanisms and would facilitate the design of effective and practical sleep deprivation treatments for depression.

The antidepressant response to partial sleep deprivation early in the night (PSD-E) was compared with the response to partial sleep deprivation late in the night (PSD-L) in 16 drug-free depressed inpatients using a balanced order crossover design. PSD-L had a significantly greater antidepressant effect than PSD-E. The response to PSD-L was sustained and enhanced by a second night of treatment. Patients had significantly shorter sleep durations and reduced REM sleep on PSD-L that did not occur on the PSD-E condition. There was a significant negative correlation between response to PSD and sleep duration, and in particular, REM sleep duration, on the late sleep deprivation condition. Thus, the amount and timing of sleep appeaar to be factors in the response to PSD, and the effect of this procedure on REm sleep may be important.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02205-02 CP

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Antidepressant Effects of Light in Seasonal Affective Disorder and Normal Controls

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | N. Rosenthal | Chief, Unit on Outpatient Studies | CPB/NIMH |
| Others: | R. Skwerer, | Medical Staff Fellow | CPB/NIMH |
| | K. Kelly, | Medical Staff Fellow | CPB/NIMH |
| | S. Kasper | Guest Researcher | CPB/NIMH |
| | P. Schulz | Social Worker | CPB/NIMH |
| | S. Rogers | Registered Nurse | CC/NURS |
| | A. Yancey | Guest Worker | CPB/NIMH |

COOPERATING UNITS *(if any)*

Morris Waxler, Ph.D., Food and Drug Administration
George Brainard, Ph.D., Jefferson Medical College

LAB/BRANCH

Clinical Psychobiology Branch

SECTION

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 2.5 | 1.5 | 1 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

We have previously shown that exposure of the eyes to bright light, but not ordinary room light, can reverse the winter depressive symptoms in patients with seasonal affective disorder (SAD). This light treatment may be effective during the morning, the evening or even during ordinary daylight hours. Normal subjects with no history of winter difficulties do not seem to benefit from this light treatment. This past year we have gone on to study whether light in a narrow band of the visual spectrum (blue or red) is as effective as the full-spectrum light used previously. We have also asked whether normal subjects who complain of mild winter difficulties might benefit from conventional bright light treatment.

In a crossover study on 21 subjects we found that although full-spectrum light tended to be be more effective than either blue or red light, this did not reach statistical significance, perhaps because the narrow-band light was clinically active to some degree. If this is so, it would suggest that the antidepressant effects of light in SAD are mediated by wavelengths that span the full visual spectrum. A separate study of full-spectrum light in 40 normal subjects, 20 with and 20 without a history of mild winter difficuties, such as low energy level or decreased productivity, showed that the former group benefited from light treatment whereas the latter group did not. The degree of improvement was related to the duration of treatment, 5 hours per day proving superior to 2 hours per day. Since there seems to be a high prevalence of normal subjects with mild winter difficulties, this finding may have widespread public health implications.

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02206-03 CP

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Neurobiology of Seasonal Affective Disorder and Light Therapy

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | N. Rosenthal | Chief, Unit on Outpatient Studies | CPB/NIMH |
| Others: | R. Skwerer | Medical Staff Fellow | CPB/NIMH |
| | F. Jacobsen | Medical Staff Fellow | CPB/NIMH |
| | K. Kelly | Medical Staff Fellow | CPB/NIMH |
| | L. Tamarkin | Research Biologist | CPB/NIMH |
| | T. Wehr | Chief, Clinical Psychobiology Branch | CPB/NIMH |
| | R. Mghir | Guest Researcher | CPB/NIMH |

COOPERATING UNITS *(if any)*

W. Berretini, BPB/NIMH, D. Jimerson, M.D., SBP/NIMH
M. Rudorfer, M.D., LCS/NIMH, E. Obarzanek, SBP/NIMH, C. Duncan, Ph.D., LPP/NIMH

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Clinical Psychobiology Branch

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INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
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| 2 | 1 | |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Although it has been established that bright light is an effective treatment for SAD, the mechanism of its action remains unknown. We have shown that our previous theory, that light works by suppressing melatonin secretion, is an unsatisfactory explanation of this form of treatment. Another theory, proposed by Lewy and colleagues, that light exerts its antidepressant effects by modifying circadian rhythms, is similarly unsatisfactory. We have continued to pursue our investigations by measuring relevant biological variables in SAD patients and normal subjects and evaluating the effects of light on these measures.

We have found several differences in patients with SAD and normals: (1) Increased mitogen stimulation of peripheral lymphocytes in both summer and winter in patients compared to normals; bright light suppresses this response in patients but enhances it in normals. (2) SAD patients show increased resting metabolic rate (RMR) in winter compared to normals, and light significantly suppresses the RMR. (3) Plasma norepinephrine levels in SAD patients are inversely proportional to the severity of their depressive symptoms, and increased norepinephrine levels are observed in response to light treatment in direct proportion to its antidepressant efficacy. (3) A similar direct relationship between treatment efficacy and a biological effect is observed in the amplitude enhancement of the P300 component of the event related potential in SAD patients, a change seen within 48 hours of beginning light therapy. (4) Brain serotonin pathways appear to be abnormally sensitive in SAD patients as measured by psychological and hormonal responses (prolactin and cortisol) to injection of the serotonin agonist, M-CPP. (5) Overnight plasma melatonin is low in SAD, as in other depressed populations. (5) Light treatment appears to delay the nadir of cortisol secretion. (6) Recent sleep studies show a shorter total sleep time and greater REM percentage and movement time in patients compared to controls. Light increases delta sleep time and sleep efficiency in patients but decreases these parameters in control subjects. These biological findings are discussed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02222-01 CP

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

The Treatment of Rapid-Cycling Manic-Depressive with Thyroxine

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | D. Sack | Chief, Inpatient Services | CPB/NIMH |
| Others: | T. Wehr | Chief, Clinical Psychobiology Branch | CPB/NIMH |
| | N. Rosenthal | Chief, Outpatient Services | CPB/NIMH |
| | W. Mendelson | Chief, Unit on Sleep Studies | CPB/NIMH |

COOPERATING UNITS *(if any)*

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Clinical Psychobiology Branch

SECTION

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 3 | 2 | 1 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

There is some evidence that the hypothalamic-pituitary-thyroid axis plays a role in the pathophysiology of affective illness, particularly in patients with rapid cycling forms of manic-depressive illness, who have a very high incidence of lithium-induced hypothyroidism. Rapid cycling patients are often refractory to standard types of mood-stabilizing treatments. Since the 1930s there have been three reports that hypermetabolic doses of thyrodxine suppress rapid cycling. These reports were based on uncontolled studies.

We treated seven rapid cycling patients with suppressive and hypermetabolic doses of thyroxine in a placebo controlled, double-blind study. No patient improved on supressive doses. Two patients remitted completely on hypermetabolic doses, but both eventually relapsed after many months of treatment. This result is interesting from a theoretical point of view, but does not seem to offer any new approach to treatment for refractory rapid cycling patients. Therefore, the project has been terminated.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02223-04-CP

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Pentobarbital and Ethanol Toxicity: Relation to the Benzodiazepine Receptor

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | W. B. Mendelson | Chief, Section on Sleep Studies | CPB/NIMH |
| Others: | J.V. Martin | Chemist | CPB/NIMH |
| | R. Wagner | Guest Worker | CPB/NIMH |

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Psychobiology Branch

SECTION

Section on Sleep Studies

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 0 | 0 | 0 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

In the course of measurements of respiration, spontaneously occurring cessations of breathing, analogous to human sleep apneas, were observed in rats. Subsequently, the apparatus for monitoring respiration was dedicated to Project #Z01-MH 02382-01 CP in order to characterize an animal model of sleep apnea. For this reason, and because the investigators left NIH in July, 1987, Project Z01 MH 02223-04-CP has been terminated.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02225-04-CP

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Studies on the Role of Calcium Flux in the Sleep-Inducing Effects of Flurazepam

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | W. B. Mendelson | Chief, Section on Sleep Studies | CPB/NIMH |
| Others: | J.V. Martin | Chemist | CPB/NIMH |
| | R. Wagner | Guest Worker | CPB/NIMH |

COOPERATING UNITS *(if any)*

S. Paul, Chief, Clinical Neuroscience Branch, NIMH
M. Majewska, Visiting Associate, Clinical Neuroscience Branch, NIMH

LAB/BRANCH

Clinical Psychobiology Branch

SECTION

Section on Sleep Studies

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 0.7 | 0.5 | 0.2 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Our previous studies have shown that there may be a functional relationship between benzodiazepine (BZ) receptor stimulation and alterations in calcium flux. Nifedipine, a calcium channel blocker, prevents the sleep-inducing effects of flurazepam in rats. Conversely, BAY K 8644, a calcium channel agonist, potentiates the effects of flurazepam on sleep. However, as we reported last year, experimental models for the anticonvulsant and anxiolytic effects of BZ's are not affected by calcium channel antagonists, indicating that calcium channels may have a more important role in sleep induction than in other actions of BZ's. The sleep-inducing effects of pentobarbital were not sensitive to inhibition by nifedipine, indicating that barbiturates may cause sleep through a mechanism that does not require changes in calcium flux. Since pentobarbital causes changes in chloride ion flux, a second mechanism for sleep induction might involve a chloride channel. To expand this line of investigation, this year we studied the effects on sleep of two steriods, which enhance chloride uptake into synaptoneurosomes in a manner similar to barbiturates.

The two steroids, 3alpha , 5alpha -tetrahydrocorticosterone (THDOC) and 3alpha -hydroxy-5alpha-dihydroprogesterone (OH-DHP), are endogenously occurring ring A metabolites of corticosterone and progesterone. Since THDOC and OH-DHP not only alter chloride flux but also enhance the binding of [$^3$H]flunitrazepam to brain membranes, we studied the effects on sleep in rats of 5 and 10 mg/kg of the steroids alone and in combination with a low dose of flurazepam. THDOC, but not OH-DHP, had potent dose-dependent sleep-inducing properties and increased nonREM sleep, but did not affect REM sleep. Flurazepam had a similar hypnotic effect but additionally reduced REM sleep. There were no significant interactions between THDOC and flurazepam.

This project was terminated in July, 1987 when the investigators in the Section on Sleep Studies left NIH.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

## NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02290-03 CP

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Melatonin analysis of clinical samples

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | L. Tamarkin | Research Biologist | CPB/NIMH |
| Others: | G. Paciotti | Biologist | CPB/NIMH |
| | M. Collins | Biologist | CPB/NIMH |

COOPERATING UNITS *(if any)*

W. Berretini and J. Nurnberger, Clinical Neurogenetics Branch, NIMH,

LAB/BRANCH

Clinical Psychobiology Branch

SECTION

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 0.2 | 0.2 | |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Melatonin has been measured in plasma and cerebrospinal fluid from human patients and normal volunteers. The findings of the studies outlined in last year's report are currently being written for submission to peer reviewed journals. The one major ongoing study is focused on the possible heritability of the increased sensitivity to light at night of children of parents with major depression.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02292-03 CP

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Melatonin Effect on Hormone-Stimulated Cell Growth

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | L. Tamarkin | Research Biologist | CPB/NIMH |

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Psychobiology Branch

SECTION

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

| | | |
|---|---|---|
| TOTAL MAN-YEARS: 0 | PROFESSIONAL: 0 | OTHER: |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Project held in abeyance

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02294-03 CP

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Antidepressant Pharmacology of the Rodent Circadian System

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | W. Duncan | Research Psychologist | CPB/NIMH |
| Others: | L. Tamarkin | Research Biologist | CPB/NIMH |
| | T. Wehr | Chief, Clinical Psychobiology Branch | CPB/NIMH |

COOPERATING UNITS *(if any)*

P. Sokolove, Professor of Biological Sciences
University of Maryland, Baltimore County (UMBC)

LAB/BRANCH

Clinical Psychobiology Branch

SECTION

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 2 | 1 | 1 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The circadian system in patients with primary affective disorder is disorganized. A major symptom of this disease includes a disturbed activity-rest cycle. Treatments which affect the circadian system may correct a pathological state which underlies depression. Our goal is to understand how antidepressant chemicals alter the dynamics of the mammalian circadian system. Results from these studies will be valuable to understand the mechanism of chemical antidepressant treatments in humans.

Previously we reported that in hamsters, clorgyline, a monoamine oxidase inhibitor with antidepressant properties, increases the period of the circadian clock and decreases the rest component of the daily activity-rest cycle. We also observed that this chemical alters the response of the circadian clock to light. These results indicate that clorgyline exhibits input properties to the circadian clock; the location of its input has been unclear.

Processing of light information to the clock occurs at either the retina or the lateral geniculate nucleus projection to the clock. Results from the past year indicate clorgyline's effects are not mediated via the retinal projection to the clock. Our current hypothesis is that clorgyline alters the hamster circadian system via a lateral geniculate nucleus projection to the circadian clock. We are currently testing this hypothesis.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02303-02 CP

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Studies of Sleep in Psychiatric Illness

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Pnncipal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | W. Mendelson | Chief, Section on Sleep Studies | CPB/NIMH |

COOPERATING UNITS *(if any)*

Clinical Psychobiology Branch

LAB/BRANCH

Section on Sleep Studies

SECTION

NIMH, NIH, Bethesda, Maryland 20892

INSTITUTE AND LOCATION

| | | |
|---|---|---|
| TOTAL MAN-YEARS:<br>1.5 | PROFESSIONAL:<br>0.3 | OTHER:<br>1.2 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

In a previous study patients with bipolar depression were compared to age and sex matched controls, there were differences in sleep efficiency and total sleep, but no differences in REM latency or power spectra. We have looked at the power spectra of insomniacs and compared it to controls. There were no differences in power spectra of insomniacs when compared to controls. Our previous studies of the frequency analysis of depressed bipolar patients compared to normal controls slowed difference in sleep efficiency and total sleep but no difference in REM latency and power spectra. We look at the power spectra of sleep in insomniacs and compared it with controls. There were no differences found in any aspect of the frequency analysis.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02324-02 CP

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Neuroendocrine Modulation of Cellular Immune Response

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | L. Tamarkin | Research Biologist | CPB/NIMH |
| Others: | G. Paciotti | Biologist | CPB/NIMH |
| | R. Skwerer | Medical Staff Fellow | CPB/NIMH |
| | M. Collins | Biologist | CPB/NIMH |

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Psychobiology Branch

SECTION

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 0.2 | 0.2 | |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The focus of this line of investigation is to compare short-term vs long-term neuroendocrine challenges on the proliferation of splenic lymphocytes. This was accomplished by comparing the in vitro proliferative response of lymphocytes to concanavalin A following an in vivo 4 hour isoproterenol treatment compared to a 5 day constant infusion of isoproterenol. Following the short-term isoproterenol treatment splenic lymphocyte proliferation was inhibited compared to controls, while long-term exposure resulted in an increase in the proliferative response. These results were not related to corticosterone levels which were elevated in both the acute and chronic treatments, nor were they related to the presence of the adrenal gland. These studies suggest that splenic lymphocytes become insensitive to the suppressive effect of chronically elevated glucocorticoid.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02325-02 CP

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Light and Lymphocyte Activity: Basic and Clinical Studies

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

| | | | |
|---|---|---|---|
| PI: | L. Tamarkin | Research Biologist | CPB/NIMH |
| Others: | R. Skwerer | Medical Staff Fellow | CPB/NIMH |
| | G. Paciotti | Biologist | CPB/NIMH |
| | M. Collins | Biologist | CPB/NIMH |
| | J. Rhyne-Grey | Biologist | CPB/NIMH |

COOPERATING UNITS (if any)

LAB/BRANCH

Clinical Psychobiology Branch

SECTION

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1.1 | 1.1 | |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

In last year's report we reported that peripheral blood lymphocytes from patients with winter depression had different in vitro responses to mitogen following bright light treatment compared to placebo treatment. This year the same study was repeated with a different group of patients and the observations were the same as that noted in the first study. To gain some further understanding of the mechanism by which light affected the cellular immune response, a group of normal volunteers was exposed to bright light or ordinary light restricted to their eyes. The data from this study were quite clear, showing that light perceived through the eyes is transduced through the central nervous system, impacting on the cellular immune response.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02326-02 CP

PERIOD COVERED
October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Behavioral Modulation of the Cellular Immune Response

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | L. Tamarkin | Research Biologist | CPB/NIMH |
| Others: | M. Collins | Biologist | CPB/NIMH |
| | R. Skwerer | Medical Staff Fellow | CPB/NIMH |
| | G. Paciotti | Biologist | CPB/NIMH |

COOPERATING UNITS *(if any)*

S. Suomi, Laboratory of Comparative Ethology, NICHD, NIH

LAB/BRANCH
Clinical Psychobiology Branch

SECTION

INSTITUTE AND LOCATION
NIMH, NIH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 0.2 | 0.2 | |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Young rhesus monkeys were placed into groups of 4 by slowly introducing them to less and less controlled environments. Blood samples were taken from awake animals in under 5 minutes and peripheral blood lymphocytes were isolated and cultured. The data from three groups of 4 indicate that the most dominant animal in the group has suppressive effect on the ability of lymphocytes to proliferate in response to mitogen in vitro.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 MH 02327-02 CP

PERIOD COVERED
October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Direct effect of Lymphokines on Cultured Human Breast Cancer Cells

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | L. Tamarkin | Research Biologist | CPB/NIMH |
| Others: | G. Paciotti | Biologist | CPB/NIMH |

COOPERATING UNITS *(if any)*

LAB/BRANCH
Clinical Psychobiology Branch

SECTION

INSTITUTE AND LOCATION
NIMH, NIH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1.0 | 1.0 | |

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Interleukin 1 and interleukin 2 are products of the immune system whose action has been almost exclusively studied in the modulation of immune cell growth. Essentially these molecules are considered paracrine hormones. Our hypothesis is that these proteins may be endocrine hormones, whose action may be on cells of non-immune origin. We have seen that both IL-1 and IL-2 affect human breast cancer cell growth and further that this action occurs on hormone-dependent breast cancer cells, but not on hormone-independent breast cancers. These studies have been conducted in vitro using $^3$H-thymidine incorporation as an index of proliferation or actual cell number. Additionally, an IL-1 receptor has been characterized on MCF-7 breast cancer cells. In vivo IL-2 has been shown to suppress tumor cell growth using athymic nude mice implanted with tumor cells and IL-2 as the model system.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02328-02 CP

PERIOD COVERED
October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Direct effects of IL-2 on Cultured Anterior Pituitaries

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

| | | | |
|---|---|---|---|
| PI: | L. Tamarkin | Research Biologist | CPB/NIMH |
| Others: | G. Paciotti | Biologist | CPB/NIMH |
| | M. Collins | Biologist | CPB/NIMH |
| | K. Nyhus | Summer Student | CPB/NIMH |

COOPERATING UNITS (if any)

LAB/BRANCH
Clinical Psychobiology Branch

SECTION

INSTITUTE AND LOCATION
NIMH, NIH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1.0 | 1.0 | |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The possibility that lymphokines affect other hormone dependent tumors, particularly tumor cells from the pituitary is the focus to this study. AtT-20 is a mouse tumor cell line that secrete ACTH and we have seen that the growth of these cells and the secretion of ACTH is affected by both IL-1 and IL-2. When tumor cell growth is inhibited, ACTH secretion per cell is increased. Conversely, when tumor cell growth is increased ACTH secretion per cell is diminished.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02382-01 CP

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

An Animal Model for Human Sleep Apnea

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

| | | | |
|---|---|---|---|
| PI: | W.B. Mendelson | Chief, Section on Sleep Studies | CPB/NIMH |
| Others: | J.V. Martin | Chemist | CPB/NIMH |
| | R. Wagner | Guest Worker | CPB/NIMH |

COOPERATING UNITS (if any)

S.I. Rapoport Chief, Laboratory of Neurosciences, NIA

LAB/BRANCH

Clinical Psychobiology Branch

SECTION

Section on Sleep Studies

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 0.9 | 0.5 | 0.4 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Using a non-invasive technique which measures respiration as a function of chest and abdominal movements, it was found that adult rats have periodic cessations in breathing analogous to human apneas. In preliminary studies in Fischer-344 rats apneas tended to be more frequent in 22-month-old than in 3-month-old rats. As in human apnea, apneas in Sprague-Dawley rats were significantly more frequent and longer in duration in REM sleep than in nonREM sleep or waking.

The project was terminated in July, 1987 when the investigators in the Section on Sleep Studies left NIH.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02383-01 CP

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Effects on Sleep of a Microinjection of Triazolam to Discrete Brain Loci

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | W.B. Mendelson | Chief, Section on Sleep Studies | CPB/NIMH |
| Others: | J.V. Martin | Chemist | CPB/NIMH |
| | H. Stevens | Psychologist | CPB/NIMH |
| | R. Wagner | Guest Worker | CPB/NIMH |

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Psychobiology Branch

SECTION

Section on Sleep Studies

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20982

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1.4 | 0.5 | 0.9 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

As part of a systematic investigation of the possible brain sites at which benzodiazepines (BZ's) alter sleep, 0.5 μg of triazolam was injected into the dorsal raphe nucleus (DRN) of rats. Injections of triazolam to the DRN significantly increased sleep latency and decreased nonREM sleep as compared to injections of vehicle to the DRN or injections of triazolam to brain areas near but outside the DRN.

This project was discontinued following departure of the investigators from NIMH in July, 1987.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 MH 02402-01 CP

PERIOD COVERED
October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Causes and Treatment of Summer Depression

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

| | | | |
|---|---|---|---|
| PI: | T. A. Wehr | Chief, Clinical Psychobiology Branch | CPB/NIMH |
| Others: | N. E. Rosenthal | Chief, Unit on Outpatient Studies | CPB/NIMH |
| | P. Schulz | Social Worker | CPB/NIMH |
| | S. Kasper | Visiting Scientist | CPB/NIMH |
| | K. Kelly | Medical Staff Fellow | CPB/NIMH |
| | J.R. Joseph-Vanderpool | Medical Staff Fellow | CPB/NIMH |

COOPERATING UNITS (if any)

LAB/BRANCH
Clinical Psychobiology Branch

SECTION

INSTITUTE AND LOCATION
NIMH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 2 | 1 | 1 |

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Seasonal patterns of affective illness are of particular interest because they suggest that environmental factors may be capable of causing and terminating affective episodes. We recently identified a group of patients who become depressed in summer and normal, or hypomanic, in winter. This pattern is opposite to one we previously described in patients who become depressed in winter, and who respond to treatment with bright artificial light. Approximately 30 summer depressives have been studied. Symptom profiles of winter and summer depression are similar in most respects, except that winter depressives usually oversleep and overeat, while summer depressives sleep less and lose weight. Both types of depression are much more common in women than in men. We tested the hypothesis that seasonal changes in light or temperature might cause summer depression, in a balanced randomization crossover study comparing possible therapeutic effects of darkness and cold. The results of the study were encouraging, in that patients improved significantly after both types of treatment. However, the results did not enable us to distinguish between the respective roles of light and temperature. We are following up with a complementary study of the capacity of heat and light to induce depressive symptoms in this population. Thyroid hormones decreased when patients became depressed in the summer. Further research is necessary to determine whether these changes are responsible for summer depressions. In nine patients, positron emission tomography (PET) scans were obtained during their summer depressions. These will be repeated during fall/winter remissions for comparison.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02403-01 CP

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Mechanism of Action of Melatonin

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | L. Tamarkin | Research Biologist | CPB/NIMH |
| Others: | G. Paciotti | Biologist | CPB/NIMH |
| | M. Collins | Biologist | CPB/NIMH |
| | J. Rhyne-Grey | Biologist | CPB/NIMH |

COOPERATING UNITS *(if any)*

Steven Reppert, Associate Professor, Children's Service, Massachusetts General Hospital
Arayan Namboodiri, Assistant Professor, Department of Biology, Georgetown University

LAB/BRANCH

Clinical Psychobiology Branch

SECTION

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 0.3 | 0.3 | |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The melatonin analog, iodo-melatonin, may provide us with an ideal agonist to identify, characterize, and localize the melatonin receptor. We have made radioactive and "cold" iodo-melatonin. This product has been characterized by HPLC and the "cold" iodo-melatonin has been shown to be biologically active. Preliminary data indicate that melatonin can displace iodo-melatonin binding to a crude supernatant of hamster brain, but no binding was observed with similarly prepared rat brain homogenate.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02405-01 CP

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Chemical Antidepressant Effects on Body Mass and Body Composition in Hamsters

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | W. Duncan | Research Psychologist | CPB/NIMH |
| Others: | T. Wehr | Chief, Clinical Psychobiology Branch | CPB/NIMH |

COOPERATING UNITS *(if any)*

T.J. Bartness, Senior Research Associate,
Worcester Foundation Experimental Biology

LAB/BRANCH

Clinical Psychobiology Branch

SECTION

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| .5 | .25 | 0 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

In humans, one of the side effects of chronic chemical antidepressant treatment is a change in body mass. The mechanism of these induced changes is not clear but may include alterations in metabolic rate, as well as effects on specific body components such as body lipid, protein or water. We have previously noted chemical antidepressant induced alterations in the body mass of Syrian hamsters being treated chronically with the monoamine oxidase inhibitor (MAOI) clorgyline. This project was undertaken to more formally explore the behavioral and physiological mechanisms responsible for these alterations in Syrian hamsters.

We have observed that initial clorgyline treatment decreases food intake. During chronic drug administration, clorgyline administration reduces the rate of weight gain although the level of food intake is not different from control. Thus, drug treated hamsters consume more food per unit of body mass than do control animals, i.e. they exhibit a negative energy balance relative to control animals.

Analysis of the carcass composition of clorgyline treated hamsters indicates that drug induced changes are due to a decrease in body lipid content, rather than protein or water. Since seasonal changes in body mass are due to fluctuations in body lipid content, our results indicate that clorgyline may be affecting the same photoperiodic process which is responsible for photoperiodic-induced changes of body mass in the Syrian hamster.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00274-13 LCS

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Methods of Ionization in Mass Spectrometry

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.: Sanford P. Markey, Chief, Section on Analytical Biochemistry, LCS, NIMH
Others: Jeffrey P. Honovich, NRC Research Associate, SAB, LCS, NIMH
Tao-Chin Wang, Fogarty Fellow, IRP, NINCDS

COOPERATING UNITS *(if any)*

Department of Pharmacology, George Washington University, Washington, DC
Oak Ridge National Laboratory, Analytical Chemistry Division, Oak Ridge, TN

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Analytical Biochemistry

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, MD 20892

| | | |
|---|---|---|
| TOTAL MAN-YEARS: 3.5 | PROFESSIONAL: 1.5 | OTHER: 2 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Mechanical and software improvements have been installed and tested on the dual cell Fourier transform ion cyclotron resonance spectrometer (FT-ICR) which have corrected many of the previously encountered problems. Laser desorption of polyethyleneglycol mixtures has been used to optimize ion optics and test ion trapping and transfer. Experiments to optimize sample sensitivity and detectability of neuropeptides are in progress.

Collaborative studies on an organic ion microprobe to image the distribution of organic substances in tissue slices are continuing at Oak Ridge National Laboratory. Collaborative studies on element and nuclide selective analyses using a microwave reaction interface for gas chromatography-mass spectrometry are in progress at George Washington University.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00276-08 LCS

PERIOD COVERED

October 1, 1985 through September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Metabolism of Melatonin

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.: Sanford P. Markey, Chief, Section on Analytical Biochemistry, LCS, NIMH

COOPERATING UNITS *(if any)*

Section on Neuroendocrinology, LDN, NICHD
Office of the Chief, LCS, NIMH
Department of Pediatrics, USUHS
Clin. Psychobiol. Branch, NIMH

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Analytical Biochemistry

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, MD 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1.0 | | 1.0 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☒ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project was inactivated early in the year and subsequently terminated.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00277-08 LCS

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Synthesis of Stable Isotope-Labeled Compounds

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.: Sanford P. Markey, Chief, Section on Analytical Biochemistry, LCS, NIMH
Others: Adrian Weisz, Visiting Fellow, LCS, NIMH
Riccardo Boni, Visiting Fellow, LCS, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Analytical Biochemistry

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, MD 20892

| | | |
|---|---|---|
| TOTAL MAN-YEARS: 1.5 | PROFESSIONAL: 1.2 | OTHER: .3 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Stable- and some radioisotope-labeled compounds have been synthesized to support other laboratory projects. Structural analogues of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) were prepared; oxygen-18-labelled-quinolinic acid prepared by exchange for use as an internal standard; synthetic routes for labelled tryptophan and its metabolites are under study.

| DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE<br>NOTICE OF INTRAMURAL RESEARCH PROJECT | PROJECT NUMBER<br>Z01 MH 00279-05 LCS |
|---|---|

PERIOD COVERED
October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Pharmacology of Neurotoxins

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.: Sanford P. Markey, Chief, Section on Analytical Biochemistry
Others: Jan Johannessen, Senior Staff Fellow, SAB, LCS, NIMH
Song-cheng Yang, Visiting Scientist, SAB, LCS, NIMH
Hiroya Ikeda, Guest Worker, SAB, LCS, NIMH
Mark Duncan, Visiting Fellow, IRP, NINCDS
Miles Herkenham, Senior Investigator, LNP, NIMH
Kris Bankiewicz, Visiting Fellow, IRP, NINCDS

COOPERATING UNITS *(if any)*
Laboratory of Neurophysiology, NIMH
Office of the Director, IRP, NINCDS

LAB/BRANCH
Laboratory of Clinical Science

SECTION
Analytical Biochemistry

INSTITUTE AND LOCATION
NIMH, ADAMHA, NIH, Bethesda, MD 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 6 | 4.5 | 1.5 |

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The mechanism of action and the metabolism of the parkinsonian-syndrome inducing neurotoxin MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) has been studied in mouse, dog, and monkey. The metabolism of radiolabelled MPTP has shown that only the pyridinum metabolite, MPP+, is accumulated in monkey brain. Distribution of that metabolite with respect to time (1, 3, or 10 days) indicated that MPP+ persists in the striatum and does not migrate toward or co-exist with the dense neuromelanin deposits in the substantia nigral cells. The conditions for the safe handling of animals treated with MPTP was evaluated; MPTP and its metabolites are not vapor borne, and treated animals can be handled safely with normal laboratory protective clothing.

The neurotoxic effects of MPTP in beagle dogs has been evaluated. MPTP produces a profound and permanent loss of cells within the substantia nigra at doses similar to those effective in primates. Dogs exhibit a transient hypokinesia, but regain locomotor capability in spite of the extent of nigral cell loss.

Immunoassay of MPTP and MPP+ has been improved and polyclonal rabbit antibodies characterized for their binding characteristics. Brain extracts contain substances with interfere with antigen-antibody recognition, necessitating chemical separation. A metabolism study of another parkinsonian producing neurotoxin, α-methyl-β-methylaminopropionic acid (BMAA) has been initiated.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

## NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02384-01 LCS

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Brain Quinolinic Acid Metabolism: Role in Neuropathology

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.: Melvyn P. Heyes, Visiting Associate, LNP, NIMH
Other: Sanford P. Markey, Chief, Section on Analytical Biochemistry, LCS, NIMH

COOPERATING UNITS *(if any)*

Laboratory of Neurophysiology

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Analytical Biochemistry

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, MD 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1.5 | 0.5 | 1.0 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Humans are afflicted with a wide variety of neurodegenerative diseases, especially of the cerbral cortex and striatum, which result in neuropsychiatric disturbances. Key anatomical and neurochemical characteristics of certain neuropathologic conditions can be replicated in experimental animals by local injections of quinolinic acid (QUIN), an endogenous metabolite of tryptophan (TRP). QUIN has proved to be a potent neurotoxin and convulsant and may therefore be involved in human neuropathology. To investigate such a role, we developed a sensitive, accurate and specific assay for QUIN in brain and cerebrospinal fluid (CSF). We found that brain QUIN is increased by systemic TRP and 3-hydroxyanthranilic acid (3-OHAA) loads. Inhibition of TRP metabolism by pyrazinamide (PYR) facilitates increases in QUIN following TRP administration. These findings are consistent with an etiologic role of QUIN in glutaric aciduria type I, a pediatric disorder associated with impaired metabolism of TRP.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

## NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00351-13-LCS

PERIOD COVERED

October 1, 1986 - September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Clinical Pharmacology of the Central Nervous System

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

David C. Jimerson, M.D., Chief, Section of Biomedical Psychiatry

COOPERATING UNITS *(if any)*

SAB, LCS, NIMH; SCBB, LCS, NIMH

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Section on Biomedical Psychiatry

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, MD 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 0.6 | 0.3 | 0.3 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Studies in the laboratory focused on the effects of altered feeding patterns, stress, and pharmacologic treatments on the regulation of appetitive behavior, satiety responses and body weight, with particular focus on the influence of central catecholamine and endogenous opiate systems. In a series of studies on the behavioral pharmacology of feeding in laboratory rodents begun during the past year, we showed that naloxone decreased sham feeding of sucrose in a dose dependent pattern similar to that produced by the dopamine antagonist pimozide. Preliminary results of a study neonatal treatment of laboratory rodents with opiate agonists demonstrated that these animals have long-lasting alterations in opiate-mediated feeding behaviors. These preclinical studies may assist in the development of animal models pertinent to the clinical disorders of bulimia and anorexia nervosa.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

## NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02289-03-LCS

PERIOD COVERED

October 1, 1986 - September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Psychobiology of Eating Disorders

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

David C. Jimerson, M.D., Chief, Section on Biomedical Psychiatry

COOPERATING UNITS *(if any)*

SCN, LCS, NIMH; SCP, LCS, NIMH; SCN, BPB, NIMH; CNG, NIMH; SCS, NSB, NIMH

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Section on Biomedical Psychiatry

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, MD 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 3.7 | 2.7 | 1.0 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
 ☐ (a1) Minors
 ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Clinical investigations involving the syndromes of bulimia and anorexia nervosa during the past year included neurotransmitter, neuropeptide, neuroendocrine, metabolic, pharmacologic and related behavioral studies on neurobiologic factors thought to contribute to the etiology of these disorders, and to their variable responsiveness to available treatments. Consistent with preclinical data implicating hypothalamic serotonin dysregulation in impaired post-prandial satiety, administration of the serotonin agonist m-chlorophenylpiperazine (m-CPP) decreased caloric intake in test meal studies. Prolactin responses to m-CPP were significantly blunted in eating disorder patients and in bulimic anorexic patients. Analysis of pharmacokinetic data showed that m-CPP-induced migraine-like headaches in eating disorder patients were related to blood level of the drug, as well as to personal and family history of migraine headache. Analysis of samples from a newly completed lumbar puncture study demonstrated that cerebrospinal fluid levels of homovanillic acid were significantly reduced in patients with severe bulimia, consistent with an alteration in central reward pathways involving dopamine. In preliminary results of a collaborative study of behavioral and neurochemical responses to 2-deoxyglucose, bulimic patients had blunted responses as reflected in hunger ratings and caloric consumption during a test meal. Follow up on our previous findings of dysregulation of opiate and hypothalamic-pituitary-adrenal function in anorexic patients included collaborative studies utilizing the opiate antagonist naloxone and a glucocorticoid antagonist. Interviews continued for the family study of bulimia. Studies on energy metabolism showed that resting metabolic rate was significantly reduced in weight stable bulimic patients, suggesting increased efficiency of energy utilization. Preliminary results indicated a substantial role of the thyroid axis in elevation of resting metabolic rate observed in anorexic patients during weight gain.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00326-14 LCS

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Clinical Neuropharmacology and Psychobiology of Depression and Mania

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Dennis L. Murphy, M.D. Chief Section on Clinical Neuropharmacology LCS NIMH

COOPERATING UNITS *(if any)*

BP, CBP, NIMH; VA Medical Center, Bronx, NY

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Section on Clinical Neuropharmacology

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

| | | |
|---|---|---|
| TOTAL MAN-YEARS:<br>0.2 | PROFESSIONAL:<br>0.1 | OTHER:<br>0.1 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This is the final, termination report on this project. No new data have been collected in the past year. The publications listed in this report were discussed in last year's annual report. Our Section's work in the area of the neuropharmacology and psychobiology of depression has been refocused during the past several years on affective symptomatology as it occurs in the context of obsessive-compulsive disorder (see annual report Z01 MH 00336) and in a comparative study of Alzheimer's disease and depression in the elderly (see annual report Z01 MH 00339).

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

## NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00332-09 LCS

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Animal Models for the Study of Neuropharmacologic Effects

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Charanjit S. Aulakh Staff Fellow, LCS, NIMH

COOPERATING UNITS *(if any)*

LCM, NIMH

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Section on Neuropharmacology

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, MD 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1.6 | 1.3 | 0.3 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Intravenous administration of the 5-$HT_{1B}$ receptor agonist m-chlorophenylpiperazine (m-CPP) to rats produced increases in plasma prolactin and corticosterone concentration and a decrease in plasma growth hormone. Short-term (2-4 days) or long-term (3 weeks) treatment with either the tricylic antidepressant imipramine or the monoamine oxidase (MAO) type A inhibiting antidepressant clorgyline did not have any significant effect on the baseline levels of either of these hormones. However, long-term but not short-term imipramine treatment potentiated m-CPP's effect on plasma prolactin, while long-term but not short-term clorgyline treatment attenuated m-CPP's prolactin effect. Neither antidepressant altered m-CPP's effects on corticosterone or growth hormone. These results indicate that various agents effective in different types of affective disorders exert differential modulatory influences on serotonergic mechanisms mediating neuroendocrine responses *in vivo*.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
**NOTICE OF INTRAMURAL RESEARCH PROJECT**

PROJECT NUMBER
Z01 MH 00336-08 LCS

PERIOD COVERED
October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
The Phenomenology and Treatment of Obsessive-Compulsive Disorder in Adults

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | | |
|---|---|---|---|---|
| PI: | T. R. Insel | Staff Physician | LCS | NIMH |
| Others: | D. L. Murphy | Chief | LCS | NIMH |
| | J. Zohar | Visiting Associate | LCS | NIMH |
| | R. Zohar-Kadouch | Visiting Fellow | LCS | NIMH |
| | C. Benkelfat | Visiting Fellow | LCS | NIMH |
| | M. Pato | Medical Staff Fellow | LCE | NICHD |

COOPERATING UNITS *(if any)*

LAB/BRANCH
Laboratory of Clinical Science, NIMH

SECTION
Section on Comparative Studies of Brain and Behavior

INSTITUTE AND LOCATION
NIMH, NIH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 3.0 | 2.7 | 0.3 |

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Obsessive-compulsive disorder has been studied from several different perspectives since this project began in 1980. During the past year, we have focused primarily on the treatment of this disorder. Previously we showed that the tricyclic antidepressant clomipramine was specifically anti-obsessional, in contrast to several other antidepressants. As clomipramine is considerably more potent than other tricyclic antidepressants in its serotonergic effects, we hypothesized that these effects might be important for its anti-obsessional properties. To test this hypothesis, we extended our earlier findings that the selective serotonin postsynaptic receptor agonist m-chlorophenylpiperazine (m-CPP) increased obsessional symptoms by retesting obsessive-compulsive disorder patients after chronic treatment with clomipramine. Following treatment, patients showed less of a response to m-CPP, suggesting that clomipramine was associated with postsynaptic subsensitivity. Furthermore, metergoline, a serotonin receptor antagonist, appeared to partly reverse the effects of chronic clomipramine treatment. These results, taken together with recent findings from other investigators correlating clinical improvement on clomipramine with changes in serotonin function, strongly suggest that the drug's serotonergic effects are integral to its clinical efficacy for obsessive-compulsive disorder.

Although we have learned much about the biochemical mechanism of clomipramine's action, results from another study reminded us of the limitations of this treatment. Of 18 patients discontinued from chronic clomipramine treatment, 17 relapsed within 7 weeks. Clearly, the drug is a treatment not a cure. Our continued follow-up studies of these patients have revealed the importance of nonpharmacologic factors in outcome.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00337-08 LCS

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Neuropharmacology of Neuroendocrine and Neurotransmitter Regulatory Mechanisms

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Dennis L. Murphy, M.D. Chief Section on Clinical Neuropharmacology LCS NIMH

COOPERATING UNITS *(if any)*

Centre for Reproductive Biology, Edinburgh, Scotland; BP and CP, NIMH;
NIB and LNRI, NINCDS

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Section on Clinical Neuropharmacology

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 3.1 | 2.0 | 1.1 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

m-Chlorophenylpiperazine (m-CPP), a direct serotonin receptor agonist, has been studied extensively this year by our group in rodents, monkeys, and humans. Neuroendocrine, temperature, cardiovascular, and behavioral effects of m-CPP have been characterized. Studies using m-CPP as a probe of serotonin CNS function in different psychiatric patient groups and during psychoactive drug treatment conditions are underway.

A distinct circadian rhythm in corticotropin releasing hormone was found in cerebrospinal fluid in a study in rhesus monkeys. This rhythm was over twelve hours out of phase with that of cortisol in cerebrospinal fluid or plasma, and is hypothesized to reflect non-hypophysiotropic functions of this peptide, which is well-known to be widely distributed in many brain areas outside of the hypothalamic-pituitary system.

Marked effects of antidepressant drugs, especially MAO-inhibitors, have been observed on plasma and cerebrospinal fluid melatonin in monkeys and humans; changes in N-acetylserotonin and serotonin accompanying diurnal melatonin rhythms have also been observed in monkey cerebrospinal fluid.

Antibodies to beta-endorphin, somatostatin and other neuropeptides have been identified and characterized in human plasma.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00339-06 LCS

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Neuropharmacology of Cognition and Mood in Geriatric Neuropsychiatry

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Trey Sunderland Chief Unit on Geriatric Psychopharmacology LCS NIMH

COOPERATING UNITS *(if any)*

LCM, NIMH; NIDA; Enzor Research Foundation

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Section on Clinical Neuropharmacology

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

| | | |
|---|---|---|
| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

A pharmacologic challenge strategy in Alzheimer patients using cholinergic and non-cholinergic agents has been the focus of this unit for a number of years. We have previously documented that Alzheimer patients are behaviorally and cognitively more sensitive to acute anticholinergic blockade with intravenous scopolamine, suggesting increased functional sensitivity compared to age-matched controls. This year, we have shown that this increased sensitivity is not seen in geriatric depressed patients, another population frequently presenting with cognitive deficits but without documented central cholinergic pathology. This functional sensitivity to anticholinergic agents in dementia patients has potential therapeutic implications, and we are now exploring the sensitivity of this population to a series of cholinergic agonists, including arecoline and nicotine.

Another major thrust of our unit has been the therapeutic usefulness of the selective monoamine oxidase inhibitor (MAOI), L-deprenyl, in dementia patients. Work from this last year has demonstrated that deprenyl has beneficial cognitive and behavioral effects in the Alzheimer population without serious side effects. In addition, study of the biochemical changes which accompany the use of this drug has been helpful in characterizing some of the possible mechanisms of action. While the therapeutic benefit was relatively small compared to the overall devastation of the illness, the positive effects were encouraging, and we are currently in the process of studying the longer-term effects of this drug in demented patients.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00433-07 LCS

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Role of Neuropeptides and Biogenic Amines in Neuroendocrine Regulation

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: J.M. Saavedra, Chief, Unit on Preclinical Neuropharmacology/LCS/NIMH

| | | | | |
|---|---|---|---|---|
| Others: | M. Aiso | VF/LCS/NIMH | F. Correa | Guggenheim Fellow |
| | E. Castren | VF/LCS/NIMH | S. Guillaume | Guest Researcher |
| | R. Cruciani | VF/LCS/NIMH | J.S. Gutkind | Int. Fogarty Fellow |
| | M. Kurihara | VF/LCS/NIMH | D. McKenna | PRAT Fellow/NIGMS |
| | K. Saito | VF/LCS/NIMH | L. Fochtmann | PRAT Fellow/NIGMS |
| | C. Gonzalez | VF/HI/NHLBI | A.J. Nazarali | Alberta Found. Fellow |

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Section on Clinical Pharmacology

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 9.0 | 7.5 | 1.5 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

With the use of quantitative autoradiography, we studied the role of neuropeptides (angiotensin II, atrial natriuretic peptide) and biogenic amines (dopamine) in the central regulation of autonomic nervous system and pituitary gland. We also studied the role of neuropeptides in the regulation of the immune response by localizing neuropeptide receptors in immune organs and immune cells and by investigating the second messenger response.

We demonstrated a role for central angiotensin II and atrial natriuretic peptide in the control of cardiovascular function. These neuropeptides may also be involved in regulation of the immune response. Specific angiotensin II and ß-adrenoceptors were quantified in the rat heart conduction system. New methods were developed to study localization and transport of $D_1$ and $D_2$ dopamine receptors in brain, and to study localization of malignant melanomas. Psychotomimetic phenylisopropylamine receptors were localized and quantified in selective brain areas.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

## NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00447-18 LCS

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Amine neurotransmitters and metabolites in mental illness

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

William Z. Potter, M.D., Ph.D., Chief, Section on Clinical Pharmacology, Laboratory of Clinical Science, NIMH

COOPERATING UNITS *(if any)*

Clinical Psychobiology Branch; Neuroscience Branch; Child Psychiatry Branch, NIMH; and Laboratory of Clinical Studies, NIAAA

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Section on Clinical Pharmacology

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 3.45 | 2.55 | .9 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

- ☐ (a1) Minors
- ☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Alterations of amine neurotransmitter systems (norepinephrine (NE), serotonin (5HT) and dopamine (DA)) have been indirectly implicated in the pathophysiology of the major mental illnesses, depression and schizophrenia. We have applied new techniques to study the interpretation of neurotransmitter measures from cerebrospinal fluid (CSF), plasma and urine from drug-free patients with affective illness and schizophrenia. New findings include the following:

1. The interrelationships between neurotransmitters as evidenced by correlations of metabolites of NE, 5HT and DA in CSF discriminate between responders and non-responders to antidepressant treatment. Moreover, the same measures appear to discriminate drug free schizophrenics from normal controls.

2. The important question of whether variations in at least one type of neurotransmitter receptor on cells obtainable from blood can be explained primarily on the basis of circulating agonist has been answered. Lymphocyte beta receptor parameters have been clearly shown to vary independently of plasma norepinephrine and epinephrine.

3. Longitudinal studies of patients with affective illness have included repeat biochemical measures in drug-free states during which mood was normal. Surprisingly, the exaggerated plasma NE response to going from a supine to standing position which is consistently noted in the depressed state persisted during the "well" state. Thus, investigation of the NE system may reveal a trait abnormality in persons susceptible to affective disorder and provide a means of identifying persons at risk.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00428-08 LCS

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Protein Carboxyl Methylation: A Post Translational Modifier of Protein Function

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: J.M. Saavedra, Chief, Unit on Preclinical Neuropharmacology/LCS/NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Section on Clinical Pharmacology

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

| | | |
|---|---|---|
| TOTAL MAN-YEARS: 0 | PROFESSIONAL: 0 | OTHER: 0 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project has been combined with Z01 MH 00433-07 LCS.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01850-10 LCS

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Clinical pharmacology of antidepressants

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

William Z. Potter, M.D., Ph.D., Chief, Section on Clinical Pharmacology, Laboratory of Clinical Science, NIMH

COOPERATING UNITS *(if any)*

Clinical Psychobiology Branch; Clinical Neuroscience Branch; and Laboratory of Clinical Studies, NIAAA

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Section on Clinical Pharmacology

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

| | | |
|---|---|---|
| TOTAL MAN-YEARS:<br>5.2 | PROFESSIONAL:<br>3.6 | OTHER:<br>1.6 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The therapeutic mechanism of action of antidepressant medications in humans remains unknown. Comparison of effects on specific neurotransmitters and their metabolites in cerebrospinal fluid (CSF), plasma and urine in the same patients continues. Findings of special interest during the last year include the following:

1. Unique effects of electroconvulsive therapy (ECT) in humans continue to emerge: unlike all antidepressant drugs studied it does not reduce whole body norepinephrine (NE) turnover as measured in urine or NE and serotonin turnover as measured by MHPG and 5HIAA, respectively, in CSF. In fact ECT increases both 5HIAA and the dopamine (DA) metabolite, HVA in CSF.
2. Based on these clinical findings we carried out experiments on ECT in rats and found a selective increase in the $D_1$ subtype of DA receptor in substantia nigra and caudate. Since ECT has been reported to have therapeutic effects in mania, psychosis and Parkinsonism as well as depression these DA effects likely have clinical and mechanistic implications.
3. In keeping with the theme that more than one neurotransmitter change is involved in antidepressant action, we have found that drugs with specific classes of initial biochemical effects have unique in vivo profiles of effects in humans only when changes of MHPG, 5HIAA and HVA are simultaneously taken into account. We have employed a 3-dimensional graph to obtain clear discrimination between five classes of drugs using these amine metabolites.
4. Alprazolam, a potent anti-anxiety agent with possible antidepressant properties, produces unusually robust decreases of ACTH and cortisol following intravenous administration. This finding may provide for a new test for the responsivity of the HPA axis; i.e. is it more difficult to suppress in certain psychiatric illnesses?

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01855-03 LCS

PERIOD COVERED

October 1, 1986, through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Central Neurochemistry Service

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

William Z. Potter, M.D., Ph.D., Chief, Section on Clinical Pharmacology, Laboratory of Clinical Science, NIMH

| | |
|---|---|
| Ivan N. Mefford, M.D. | Special Expert/LCS/NIMH |
| Sanford P. Markey, M.D. | Chief/AB/LCS/NIMH |

COOPERATING UNITS *(if any)*

Section on Analytical Biochemistry and Section on Biomedical Psychiatry, LCS, NIH; Laboratory of Clinical Studies, NIAAA

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Section on Clinical Pharmacology

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 4.2 | 0.7 | 3.5 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The central neurochemistry service functions as a centralized laboratory for analysis of neurotransmitters and metabolites in body fluids collected within the intramural program. routine analysis include norepinephrine in plasma urine and cerebrospinal fluid (CSF), epinephrine in plasma urine and CSF, dopamine and dopamine sulfate in urine, plasma and CSF, catecholamine metabolites, HVA, MHPG and DOPAC in CSF, plasma and urine, serotonin in platelets, platelet poor plasma and CSF and 5-HIAA in plasma, CSF and urine. GC-MS assays are used for total urinary norepinephrine, epinephrine, dopamine, VMA, MHPG, HVA, DOPAC, metanephrine and normetanephrine. HPLC with amperometric detection is used for all other assays. Implemetation of microbore HPLC analysis using novel sufactant chromatographic approaches allows measurement of free catecholamines as well as serotonin in CSF. This allows examination of duirnal rhythms and of drug effects on these amines in extracellular fluid. Some 16,000 assays were performed on over 8,000 samples which were processed during the last year.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01860-01 LCS

PERIOD COVERED
October 1, 1986, through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
The Role of Epinephrine in Brain

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Ivan N. Mefford, Ph.D.

COOPERATING UNITS *(if any)*

Section on Analytical Biochemistry and Section on Biomedical Psychiatry, LCS, NIH; Laboratory of Clinical Studies, NIAAA

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Section on Clinical Pharmacology

INSTITUTE AND LOCATION

NIH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 0.3 | 0.3 | 0 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Epinephrine is the least prevalent catecholamine in mammalian brain, localized in the most primitive and medial aspects. Traditional approaches to studying epinephrine in brain have treated it primarily as a neurotransmitter. Over the past two years our view has changed, to consider epinephrine primarily as an extraneuronal metabolite of norepinephrine, thus functioning as hormone in forebrain. This has prompted the study of the role of epinephrine in sedation and intoxication and the implementation of equilibrium dialysis as a method for monitoring extracellular fluid (ECF) epinephrine content. Inhibition of the epinephrine forming enzyme, phenylethanolamine-N-methyltransferase (PNMT) produced a potent and long-lasting antagonism of both barbiturate and ethanol intoxication in rats. ECF epinephrine exceeds norepinephrine at baseline throughout the hypothalamus in the anethestized rat, suggesting that epinephrine may act as the primary agonist as extrajunctional alpha$_2$ receptors in this part of the brain. Monitoring CSF epinephrine in rhesus monkeys demonstrates marked increases in epinephrine content during barbituratate infusion, consistent with this hypothesis.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

## NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00787-08 LCS

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Brain Mechanisms of Isolation Call in Squirrel Monkey (Saimiri sciureus)

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | P. D. MacLean | Intramural Research Scientist | LCS, NIMH |
| Other: | J. D. Newman | Research Physiologist | LCE, NICHD |

COOPERATING UNITS *(if any)*

Laboratory of Comparative Ethology, NICHD

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Section on Comparative Studies of Brain and Behavior

INSTITUTE AND LOCATION

NIMH, NIH, Poolesville, Maryland 20837

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 0.7 | 0.4 | 0.3 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

There are indications that in the therapsid-mammalian transition changes in the auditory and vocal apparatus afforded audiovocal communication as a means of maintaining maternal-offspring contact and contact of members of a group. The just completed present project is part of an investigation concerned with identifying the cerebral representation of the separation call, a basic mammalian vocalization that serves the above noted functions. For this purpose, squirrel monkeys are tested for their ability to produce spontaneous calls in isolation before and after ablations of different parts of the brain. The present study has focused on the midline frontolimbic cortex, one of two cortical areas where stimulation elicits vocalization in monkeys. Evidence derived by the process of elimination indicates that the spontaneous calls depend on the concerted action of a continuous band of rostral limbic cortex comprising parts of areas 24, 25, and 12. Ablation of the midline frontal neocortex peripheral to this limbic zone is compatible with criterion performance in the production of the call. The present report also includes ancillary observations in regard to separation calls emitted while the subject is awakening from sodium pentobarbital (Nembutal) anesthesia, as well as following the intraventricular administration of oxytocin.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00796-02 LCS

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Cytochemical Tracing of Thalamic Connections with Midline Frontal Cortex

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: P. D. MacLean Intramural Research Scientist LCS, NIMH

Other:

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Section on Comparative Studies of Brain and Behavior

INSTITUTE AND LOCATION

NIMH, NIH, Poolesville, Maryland 20837

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 0.6 | 0.3 | 0.3 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

In a parent project on the cerebral representation of the separation call (see Z01 MH 00787-08 LCS), it was found that ablation of the midline frontal cortex caudal to the polar area in squirrel monkeys did not (as was also known in the case of rhesus monkeys) result in discernible retrograde degeneration in the thalamus. The present project is employing cytochemical tracing techniques for obtaining clarification of this matter. Last year's report included a description of diverse thalamic nuclei, as well as extrathalamic structures, shown to be connected with different midline frontal areas. The present report focuses on additional findings suggesting an orderly projection of respective parts of the ventral anterior nucleus to different midline frontal areas. In the light of assorted experimental and clinical evidence that the thalamocingulate division of the limbic system and the striopallidonigral thalamic connections are implicated in crying and laughter, the anatomical findings suggest a link-up of mechanisms implicated in both the affect and expression of these manifestations.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00797-02 LCS

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Neurobiology of Attachment

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | | |
|---|---|---|---|---|
| PI: | T. R. Insel | Staff Physician | LCS | NIMH |
| Others: | L. P. Miller | Guest Worker | LCS | NIMH |

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Clinical Science, NIMH

SECTION

Section on Comparative Studies of Brain and Behavior

INSTITUTE AND LOCATION

NIMH, NIH, Poolesville, Maryland 20837

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1.3 | 0.5 | 0.8 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This is the second year of this project which investigates attachment and separation in infants and parents. Studies in rat pups have focused on the ultrasonic isolation call as a behavioral measure of separation distress. Following up on our earlier results demonstrating potent effects of the benzodiazepines on ultrasonic isolation calls during this year, we demonstrated increased occupancy of benzodiazepine receptors with in vivo receptor autoradiography during separation. These new results suggest a physiologic role for this receptor system in the separation response. We are currently testing this hypothesis further using intraventricular injections of endogenous benzodiazepine ligands into 1-week-old rat pups to investiate effects on the rate of isolation calls.

Our continuing studies of parental behavior have demonstrated that the brain is a target organ for the neuropeptide oxytocin and that oxytocin receptors increase in selected limbic regions during the postpartum period. As lesions in these regions slightly facilitate maternal behavior, oxytocin may inhibit rather than increase neural activity at these sites.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00798-01 LCS

PERIOD COVERED

February 1, 1987 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Studies on the Development of the Cerebral Cortex

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | B. B. Stanfield | Special Expert | LCS NIMH |

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Clinical Science, NIMH

SECTION

Section on Comparative Studies of Brain and Behavior

INSTITUTE AND LOCATION

NIMH, NIHAC, Poolesville, Maryland 20837

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 0.57 | 0.40 | 0.17 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects
  ☐ (a1) Minors
  ☐ (a2) Interviews

☐ (b) Human tissues

☒ (c) Neither

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project comprises ongoing studies previously supported extramurally which are being continued in the LCS as well as studies initiated since the PI joined the LCS on February 1, 1987. This work on the development of the cerebral cortex which relies heavily on neuroanatomical techniques focuses on the role of eliminatory events which occur during normal brain development. Much of our effort has concentrated on the transient occipital cortical component of the pyramidal tract which we previously identified. We have recently found that in animals in which the occipital cortex receives an induced aberrant somatosensory input through the lateral geniculate nucleus as a result of neonatal enucleation and rostral cortical lesion, some occipital neurons will maintain a spinal projection. In addition, we have recently identified axonal eliminatory phenomena which occur during the development of the fornix, of the projections of the locus coeruleus, and of the major ascending thalamic afferent systems. Finally, we have continued our studies of the projections extended and maintained by heterotopic cortical transplants made during development. All of our findings in these experiments point to cortical locale as a decisive factor in determining which of the initially extended projections a cortical neuron will maintain.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00799-01 LCS

PERIOD COVERED

February 1, 1987 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Studies on Postnatal Neuronogenesis

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | | |
|---|---|---|---|---|
| PI: | B.B. Stanfield | Special Expert | LCS | NIMH |
| Others: | T.R. Insel | Staff Physician | LCS | NIMH |

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Clinical Science, NIMH

SECTION

Section on Comparative Studies of Brain and Behavior

INSTITUTE AND LOCATION

NIMH, NIHAC, Poolesville, Maryland 20837

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 0.37 | 0.27 | 0.10 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project comprises work previously supported extramurally which is being continued in the LCS as well as studies initiated since the PI joined the LCS on February 1, 1987. These studies have utilized $^3$H-thymidine autoradiography and neuroanatomical tract tracing techniques to study aspects of the continuing neuronogenesis in the adult dentate gyrus. We have found that dentate granule cells generated in the adult rat can extend axonal projections for appreciable distances, and we have initiated a study in pygmy marmosets to see if new granule cells are generated in an adult primate.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

**NOTICE OF INTRAMURAL RESEARCH PROJECT**

PROJECT NUMBER

Z01 MH 02219-04 LCS

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Animal Models of Anxiety

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: T. R. Insel Staff Physician LCS, NIMH

COOPERATING UNITS *(if any)*

Laboratory of Comparative Ethology, NICHD; Addiction Research Center, NIDA, NIDA, Baltimore, MD

LAB/BRANCH

Laboratory of Clinical Science, NIMH

SECTION

Section on Comparative Studies of Brain and Behavior

INSTITUTE AND LOCATION

NIMH, NIH, Poolesville, Maryland 20837

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1.3 | 0.5 | 0.8 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Our approach to the neurobiology of anxiety continues to be developmental with a focus on the role of early experience on the development of neurotransmitter and neuropeptide systems. We tested a specific hypothesis: that early stress activates brain corticotropin releasing factor (CRF) pathways and has long-term effects on brain CRF receptors with mixed results. As part of this project the development of CRF neurons, receptors, and second messenger was determined in fetal and postnatal rat brain. Receptors were found to be dramatically increased over adult levels soon after birth. Treating infants with CRF had short-term effects on development, long-term effects on behavior, but no lasting effects on brain CRF receptors. In related studies, neither noradrenergic lesions nor the behavioral paradigm of learned helplessness was found to alter brain CRF receptors.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00388-11 LCS

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Coexistence of Peptides and Neurotransmitters

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | |
|---|---|---|
| David M. Jacobowitz | Chief, Histopharmacology Section | LCS, NIMH |
| Toshio Ohhashi | Guest Worker | LCS, NIMH |

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Histopharmacology

INSTITUTE AND LOCATION

NIMH, ADAMHA, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1.6 | 1.2 | .4 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Immunohistochemical studies have revealed that calcitonin gene-related peptide (CGRP) coexists with acetylcholine in motor cells of the spinal cord. Therefore this study was undertaken to investigate a possible interaction between the cholinergic nerve neurotransmitter and CGRP on neuromuscular transmission in the isolated rat diaphragm. Electrical stimulation of the isolated phrenic nerve resulted in twitch contractions which were dose-dependently potentiated by CGRP in concentrations ranging from 1.2 X $10^{-9}$ M to 3 X $10^{-7}$ M. The potentiating action of CGRP (3 X $10^{-7}$ M) returned to control level in about 25 min and was rarely tachyphylactic. The action of CGRP was dependent upon the stimulation pulse width ranging from 0.2 to 1.0 msec. Rat calcitonin (4.5 X $10^{-7}$ M) caused a minimal change in the amplitude of twitch contractions. CGRP had no effect on the quiescent striated muscle. Twitch responses to direct electrical stimulation was also enhanced by CGRP (6 X $10^{-8}$ M - 6 X $10^{-7}$ M) in the absence and presence of $10^{-5}$ M d-tubocurarine. These results suggest that CGRP modulates the action of acetylcholine at the motor-end plates of striated muscle. The possibility that an alteration in the normal peptide content in nerve endings (motor-end plates) of the body may lead to a variety of muscle malfunctions is of great clinical significance and should be studied in humans.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00396-09 LCS

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

A Study of Proteins Within the CNS by Two-Dimensional Gel Electrophoresis

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | |
|---|---|---|
| David M. Jacobowitz | Chief, Histopharmacology Section | LCS, NIMH |
| William E. Heydorn | Pharmacologist | FDA |
| Anne-Marie O'Carroll | Visiting Fellow | LCS, NIMH |
| Takemi Fukuda | Guest Researcher | LCS, NIMH |
| Lois Winsky | Guest Researcher | LCS, NIMH |
| Jitendra Patel | Visting Associate | BPB, NIMH |

COOPERATING UNITS *(if any)*

Division of Neuropharmacological Drug Products, Food and Drug Administration

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Histopharmacology

INSTITUTE AND LOCATION

NIMH, ADAMHA, Bethesda, Maryland 20205

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 3.4 | 2.4 | 1.0 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The identification of interesting proteins within the CNS utilizing 2-dimensional gel electrophoresis (2DE) continues. 1) One of the largest proteins on our brain gels, "protein 36" has been isolated and purified from homogenates of rat brain. Protein 36 is a homodimer with a molecular weight of 64 kD and a monomeric weight of 37 kD with a pI of 6.5. Immunocytochemical studies using a rabbit antibody raised to this protein revealed that protein 36 is localized in large pyramidal cells, dendrites and axons of layer V of the cerebral cortex. 2) A second protein ("protein 94") has been isolated from the bovine brain and purified. This is a cAMP-stimulated phosphoprotein (M.W. 94 kD) which was originally identified in the rat neostriatum. Purification was monitored by autoradiography of $^{32}$P-phosphorylated samples separated by SDS-PAGE. Immunocytochemical studies revealed that protein 94 was localized in astrocytes. 3) We have detected at least 3 Ca$^{++}$-binding proteins in the rat cortex by $^{45}$Ca$^{++}$ autoradiography. Two proteins were identified as calmodulin and the B subunit of calcineurin. In addition, an unidentified Ca$^{++}$-binding protein of molecular weight about 18 kD and pI 5.4 was revealed. 4) Seven high affinity calcium binding proteins have been detected following ammonium sulfate precipitation. Three of the proteins have been identified (calmodulin, B subunit of calcineurin and vitamin D-dependent calcium binding protein). The identity of the other 4 proteins are unknown. 5) We have studied phosphoproteins present in seven discrete microdissected brain areas. Marked regional differences in the pattern of phosphorylation among the brain areas studied under basal conditions and following activation of cyclic AMP-dependent protein kinase and calcium/calmodulin-dependent protein kinase and protein kinase C were noted. 6) A series of studies examining proteins within auditory nuclei are under progress. Results indicate several differences in proteins visible on two-dimensional gels across auditory nuclei or more generally between sensory nuclei and other brain areas.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

**NOTICE OF INTRAMURAL RESEARCH PROJECT**

PROJECT NUMBER
Z01 MH 00397-09 LCS

PERIOD COVERED
October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Autoimmune Aspects of Disease

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | |
|---|---|---|
| James S. Frazier | Staff Fellow | LCS, NIMH |
| Hiroyasu Nakata | Visiting Scientist | LCS, NIMH |
| David M. Jacobowitz | Chief, Histopharmacology Section | LCS, NIMH |

COOPERATING UNITS *(if any)*

LAB/BRANCH
Laboratory of Clinical Science

SECTION
Histopharmacology

INSTITUTE AND LOCATION
NIMH, ADAMHA, Bethesda, Maryland 20892

| | | |
|---|---|---|
| TOTAL MAN-YEARS: 1.3 | PROFESSIONAL: 1.1 | OTHER: .2 |

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Autoimmunity has been implicated in an increasing number of diseases including psychiatric disease. Using 2D gel electrophoresis and Western immunoblotting techniques, the study of CNS proteins continue as we look for specific proteins which might be target antigens for autoantibodies of pathologic origin. First, we have found that there exists a number of autoantibodies in the sera of noraml animals and humans that react with brain cortical proteins. These include antibodies to: the cytoskeletal proteins actin, tubulin and GFAP; the enzymes sGOT and neuron specific enolase; and the β-subunit of the signal transducing G protein. Second, we have found there to be no obvious differences between the autoantibodies seen in normals and those seen in schizophrenics. Third, we have documented the presence in a small percentage of Type I diabetics of an antibody to a 25,000 MW pancreatic specific protein. Fourth, we have purified and partially characterized this protein. And fifth, have raised a rabbit antibody that was shown by immunocytochemistry to specifically bind to islet cells of the monkey pancreas.

| | |
|---|---|
| DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE<br>**NOTICE OF INTRAMURAL RESEARCH PROJECT** | PROJECT NUMBER<br>Z01 MH 02377-01 LCS |

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

A Study of Adenosine Receptors: Isolation and Characterization

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | |
|---|---|---|
| Hiroyasu Nakata | Visiting Scientist | LCS, NIMH |
| David M. Jacobowitz | Chief, Histopharmacology Section | LCS, NIMH |

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Histopharmacology

INSTITUTE AND LOCATION

NIMH, ADAMHA, Bethesda, Maryland 20892

| | | |
|---|---|---|
| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Isolation of $A_2$ adenosine receptors from rat brain membranes have been performed. The purification methods included solubilization by digitonin and column chromatographies using Q-Sepharose, hydroxylapatite, Green A-agarose and Mono Q. Approximately 1000-fold purification was achieved at the last stage of purification and the specific binding activity of the final preparation was ∿ 100 pmol/mg protein assayed using $[^3H]$N-ethylcarboxamideadenosine (NECA) as a ligand. The apparent molecular weight of the partially purified $A_2$ adenosine receptors was estimated to be approximately 80,000 by HPLC (TSK 4000PW-5000PW) experiments.

It was also found that $A_2$ adenosine receptors could be separated from $A_1$ adenosine receptors or other unknown adenosine binding sites by hydroxylapatite chromatography.

Mouse mastocytoma P815 cell membranes were demonstrated to have $A_2$ adenosine binding sites in a relatively high concentration. These adenosine binding sites were also solubilized by detergents without any significant changes of ligand binding properties.

| | |
|---|---|
| DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE<br>NOTICE OF INTRAMURAL RESEARCH PROJECT | PROJECT NUMBER<br>Z01 MH 02239-03 LCS |

PERIOD COVERED
October 1, 1986 to September 31, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Conceptual Analysis of Complex Biobehavioral Population Systems

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*
John B. Calhoun Chief URBS LCS NIMH

COOPERATING UNITS *(if any)*
None

LAB/BRANCH
Laboratory of Clinical Science

SECTION
Section on Clinical Neuropharmacology

INSTITUTE AND LOCATION
NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 3.0 | 1.0 | 2.0 |

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project has been terminated due to the retirement of the principal investigator.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00153-10 CHP

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Treatment of Obsessional Children and Adolescents with Clomipramine

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Judith L. Rapoport, M.D., Chief, CHP, NIMH
Henrietta Leonard, M.D., NRSA Fellow, CHP, NIMH
Dennis L. Murphy, M.D., Chief, LCS, NIMH
Theodore Zahn, Ph.D., Research Psychologist, LPP, NIMH
Agnes Whitaker, M.D., Columbia University
Susan Swedo, M.D., Staff Fellow, CHP, NIMH
Martha Denckla, M.D., Chief, Autism & Behav. Dis. Sec., DNB, NINCDS
Robert Freiland, M.D., LN, NIA

COOPERATING UNITS *(if any)*

Laboratory of Psychology and Psychopathology, NIMH; Clinical Neuropharmacology Branch, NIMH; National Institute of Neurological & Communicative Disorders & Stroke; Columbia University

LAB/BRANCH

Child Psychiatry Branch

SECTION

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 3.8 | 2.3 | 1.5 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☒ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Obsessive Compulsive Disorder (OCD) is now recognized as a common mental disorder, occurring in perhaps three million people in this country alone. In adolescents, the prevalence maybe as high as one percent.

Follow-up studies in our Branch show a chronic course for the disorder with increasing severity of depression and anxiety over time. Clomipramine has a highly specific beneficial effect on obsessions while Desmethylimipramine (DMI) another tricyclic antidepressant did not differ from placebo.

New studies with brain imaging (PET and CT scan), as well as a survey of patients with Sydenham's chorea, implicate abnormalities in the basal ganglia while spinal fluid studies show that low concentration of CSF 5-HIAA, the major serotonin metabolite, is associated with more severe OCD.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

**NOTICE OF INTRAMURAL RESEARCH PROJECT**

PROJECT NUMBER

Z01 MH 00161-09 CHP

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Behavioral Effects of Dietary Substances in Normal and Hyperactive Children

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Markus Kruesi, M.D., Senior Staff Fellow, CHP, NIMH
Martine Flament, M.D., Guest Researcher, CHP, NIMH
Marian Yarrow, Ph.D., LDP, NIMH
Carolyn Zahn-Waxler, M.D., LDP, NIMH
Thomas Uhde, M.D., BPB, NIMH

COOPERATING UNITS *(if any)*

Laboratory of Developmental Psychology, NIMH
Biological Psychiatry Branch, NIMH

LAB/BRANCH

Child Psychiatry Branch

SECTION

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

| | | |
|---|---|---|
| TOTAL MAN-YEARS: .75 | PROFESSIONAL: .50 | OTHER: .25 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☒ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Relationships between aggression, activity, sugar, and aspartame were investigated in 30 preschool boys: 18 had histories of behavioral reactions to sugar and 12 were familiar peers whose parents reported their children were not sugar reactive. Analysis of week long diet diaries found no significant differences in sugar or carbohydrate consumption between the two groups nor were correlations reported previously by another group between weekly sugar consumption and observed activity and aggression replicated. Furthermore, aggression did not increase in response in blinded sugar challenge. A significant statistical but negligible decrease in actometer activity was observed following aspartame. The likelihood of behavioral reactions to aspartame seem questionable.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

## NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00178-06 CHP

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Brain Structure and Function in Developmental Neuropsychiatric Disorders

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Judith M. Rumsey, Ph.D., Staff Fellow, CHP, NIMH
Susan Swedo, M.D., Staff Fellow, CHP, NIMH
Connie Duncan, Ph.D., Staff Fellow, LPP, NIMH
Richard Coppola, Ph.D., LPP, NIMH
Daniel Weinberger, M.D., Chief, CBDB, NIMH
Martha Denckla, M.D., Chief, Autism & Behav. Dis. Sec., DNB, NINCDS
Michael Goldberg, M.D., LSR, NEI

COOPERATING UNITS *(if any)*

Laboratory of Psychology and Psychopathology, NIMH; Sec. on Autism & Behav. Dis., DNB, NINCDS; Clinical Brain Disorders Branch, NIMH; Lab. of Sensorimotor Research, NEI

LAB/BRANCH

Child Psychiatry Branch

SECTION

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 3.1 | 1.20 | 1.80 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☒ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Regional cerebral blood flow data, using a xenon inhalation technique, shows an increased hemispheric asymmetry and reduced antero-posterior difference in severe and persistent dyslexia. Analysis of EEG spectra, event-related potentials, and neuropsychological testing is in progress. Preliminary eye movement data has been collected on adults with poor reading and adults with attention deficit disorder, residual type (ADD-RT) to see if saccadic intrusions and related variables differentiate these groups. Tasks were designed for use in PET studies of dyslexic, ADD-RT, and autistic subjects. These include a phonological and a syntactic task designed to activate left perisylvian cortex, environmental sounds, timbre and tonal memory tasks designed to activate right temporal regions, attentional tasks designed to activate frontal cortex, and affective and attentional-shift tasks designed to tap into deficits associated with autism.

The sample of autistic men previously studied with PET and the fluorodeoxyglucose technique was increased, and a correlational pattern analysis of glucose metabolic data completed. Main findings were fewer large positive correlations between frontal and parietal regions and lower correlations of thalamus, caudate, lenticular nucleus, and insula with frontal and parietal regions in autistic patients, relative to controls.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

## NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00301-05 CHP

PERIOD COVERED

October 1, 1986 to September 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Diagnosis in Child Psychiatry

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Judith L. Rapoport, M.D., Chief, CHP, NIMH
Breck Borcherding, M.D., Clinical Associate, CHP, NIMH
Alan J. Zametkin, M.D., Staff Psychiatrist, CHP, NIMH
Eric Taylor, M.D., Sr. Registrar, Maudsley Hospital, London, Eng.
James Swanson, Ph.D., Prof. of Psychology, Univ .of Calif.,Irvine, CA
Michael Rutter, M.D., Prof. of Child Psychiatry, Maudsley Hospital, London, Eng.

COOPERATING UNITS *(if any)*

Department of Psychiatry, Maudsley Hospital, London, Eng.
Department of Pediatrics, University of California, Irvine, CA

LAB/BRANCH

Child Psychiatry Branch

SECTION

NSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| .30 | .20 | .10 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☒ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

To investigate the basis for widely separate rates in the diagnosis of childhood hyperactivity between the U.S. and U.K., research teams and clinician panels in both countries completed diagnostic ratings of standardized case histories using DSM III and ICD 9 diagnostic schemes. The results showed effects of diagnostic schemes on rates for the diagnosis of hyperactivity.

However, there was additional effect of nationality of case, with U.S. cases more likely to receive the diagnosis of Attention Deficit Disorder. To pursue this, a new study is started comparing 24 hour motor activity in hyperactive children and their parents in three settings: Bethesda, Maryland; Irvine, California; and London, England.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

## NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02240-03 CHP

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Neurobiology of Attention Deficit Disorder

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Judith L. Rapoport, M.D., Chief, CHP, NIMH
Alan J. Zametkin, M.D., Staff Psychiatrist, CHP, NIMH
Markus J.P. Kruesi, M.D., Staff Psychiatrist, CHP, NIMH
William Z. Potter, M.D., Ph.D., Chief, Section on Clinical Pharmacology, LCS, NIMH
Markku Linnoila, M.D., Ph.D., Chief, LCS, NIAAA
Robert M. Cohen, M.D., Ph.D., Chief, Section on Clinical Brain Imaging, LCM, NIMH

COOPERATING UNITS *(if any)*

Section on Clinical Pharmacology, LCS, NIMH
National Institute on Alcohol Abuse and Alcoholism
Section on Clinical Brain Imaging, LCM, NIMH

LAB/BRANCH

Child Psychiatry Branch

SECTION

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

| | | |
|---|---|---|
| TOTAL MAN-YEARS:<br>2.75 | PROFESSIONAL:<br>2.0 | OTHER:<br>.75 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
 ☒ (a1) Minors
 ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

To localize possible abnormal patterns of cerebral glucose metabolism and cerebral blood flow in adults with Attention Deficit Disorder (ADD) Residual Type, parents of diagnosed hyperactive children are being studied using the 2-deoxyfluoroglucose method of Positron Emission Tomography (PET).

To date, 30 PET scans have been performed without medication and 16 scans have been done during treatment with dextroamphetamine. To understand the mechanism of action of stimulant medication in the treatment of Attention Deficit Disorder with Hyperactivity (ADDH), a comparison of pemoline (Cylert), methylphenidate, and dextroamphetamine was initiated to examine the acute and chronic effects of these medications in the same subjects on peripheral measures of dopamine, norepinephrine, prolactin, and growth hormone.

The relationships between the behavioral dimensions of impulsivity, aggression, and concentrations of monoamine metabolites, particularly 5-HIAA, in the spinal fluid of children with conduct disorder and/or attention deficit disorder, is being examined. Associations between decreased CSF 5-HIAA concentrations and impulsive aggressive behavior have been reported in impulsive adults. Peripheral measures of serotonin and catecholamines are being obtained along with personality, impulsivity and aggression measures. Seventeen subjects have been studied to date. A preliminary comparison between ten Conduct Disorder and ten age-matched Obsessive Compulsive children, shows a trend ($p = .09$) for lower CSF 5-HIAA concentration in conduct disorder. Within the conduct disorder sample, lower values are associated with more destructive behavior.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00084-13 CNG

PERIOD COVERED
October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Genetic-Biologic Studies of Psychiatric Disorders

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| P.I. | E. Gershon | Chief | CNG, NIMH |
| Others: | W.H. Berrettini | Medical Officer | CNG, NIMH |
| | L. DeLisi | Asst. Professor | SUNY at Stony Brook |
| | J.I. Nurnberger Jr. | Dir. of Res., Inst. of Psych. Res., Indiana U. | |
| | J. Hamovit | Research Social Worker | CNG, NIMH |
| | J. Guroff | Social Science Analyst | CNG, NIMH |
| | D. Kazuba | Psychologist | CNG, NIMH |

COOPERATING UNITS *(if any)*
LCS, NSB, NIMH, Chestnut Lodge, Rockville, MD

LAB/BRANCH
Clinical Neurogenetics Branch

SECTION
Section on Clinical Genetics

INSTITUTE AND LOCATION
NIMH, Bethesda, MD 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 8.8 | 4.5 | 4.3 |

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Family study of schizophrenia: 108 relatives of chronic schizophrenics, 129 relatives of chronic psychosis schizoaffectives, and 380 relatives of psychiatrically normal controls, were studied with systematic diagnostic interviews, information from relatives, and review of medical records where appropriate. Comparing relatives of schizophrenics with relatives of schizoaffectives, there was no tendency for schizoaffective diagnosis or actue or chronic psychoses to aggregate separately. Increased bipolar disorder was found in relatives of schizoaffectives but not in relatives of schizophrenics. Major affective disorder (bipolar and unipolar) was increased in relatives of both types of psychotic proband. A separate family study of bulimia is ongoing.

Cultured lymphoblastoid cell lines have been prepared from a series of 40 affected-sib-groups with schizophrenia, 16 pedigrees of bipolars, and 5 schizophrenia pedigrees. These are being used in genetic linkage and association studies.

Mathematical analysis of the power of linkage methods has provided estimates of the robustness, in the presence of genetic heterogeneity, of the affected-sib-pair and pedigree lod score linkage methods (study of unaffected offspring) for inherited quantitative traits. We have also analyzed the power of the high-risk paradigm. These analyses allow precise estimates of the required numbers of individuals for valid linkage and high risk studies.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00086 11-CNG

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Outpatient Clinic for Genetic and Pharmacologic Studies of Affective Disorders

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | W.H. Berrettini | Medical Officer | CNG, NIMH |
| Others: | L. DeLisi | Asst. Professor | SUNY at Stony Brook |
| | E.S. Gershon | Chief | CNG, NIMH |
| | S. Simmons-Alling | Clinical Nurse Expert | CC, NIH |
| | J.R. Hamovit | Research Social Worker | CNG, NIMH |
| | M.E. Maxwell | Research Social Worker | CNG, NIMH |

COOPERATING UNITS *(if any)*

CC, NIH: CHP, BPB, LPP, LCS, NPB, LCS, NIMH: Catholic University: NSB, NIAA: University of Pittsburgh: Karolinska Institute: LSN, NIA: Indiana University

LAB/BRANCH

Clinical Neurogenetics Branch

SECTION

Section on Clinical Genetics

INSTITUTE AND LOCATION

NIMH, Bethesda, MD 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 3.8 | 1.5 | 2.3 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The high-risk study of healthy adolescent offspring of bipolar parents has identified a potential vulnerability marker in the at-risk population. The high-risk group shows supersensitivity to the inhibitory effects of light on plasma melatonin, suggesting that this finding may represent a genetic vulnerability marker for affective disorder.

We have completed a study of cholinergic induction of rapid eye movement (REM) sleep in euthymic unmedicated bipolars. The bipolars showed more rapid induction of REM sleep than did matched controls, confirming previous observations and providing additional evidence that cholinergic supersensitivity may be a genetic vulnerability marker for affective disorder.

Studies of the growth hormone response to clonidine in euthymic unmedicated bipolars suggest that this response is blunted in bipolar subjects compared to controls. The possibility that this represents a genetic vulnerability marker is currently being evaluated.

Studies of CSF neuropeptides in normal monozygotic and dizygotic twins have shown that neuropeptide Y levels are heritable, are high in underweight anorectics and are normal in depressives. Additionally, the related neuropeptide, peptide YY, is elevated in CSF from bulimic subjects. Galanin levels in CSF are normal in Alzheimer's Disease, depression and eating disorders.

Acute IV administration of physostigmine produces increases in CSF neuropeptide Y, in both monkeys and man, indicating that pharmacologic challenges may employ CSF neuropeptide levels in assessing the drug effect on various CNS neurotransmitters.

| DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE<br>NOTICE OF INTRAMURAL RESEARCH PROJECT | PROJECT NUMBER<br>Z01 MH 02236-03 CNG |
|---|---|

PERIOD COVERED
October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Schizophrenia Studies

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| P.I.: | L.E. DeLisi | Staff Psychiatrist | CNG, NIMH |
| Others: | E.S. Gershon | Chief | CNG, NIMH |
| | L.R. Goldin | Senior Staff Fellow | CNG, NIMH |
| | C.W. Dingman | Staff Psychiatrist | Chestnut Lodge |
| | I.D. Dauphinais | NRSA Fellow | CNG, NIMH |
| | M.E. Maxwell | Research Social Worker | CNG, NIMH |
| | J.R. Hamovit | Research Social Worker | CNG, NIMH |

COOPERATING UNITS *(if any)*
Springfield Hospital; Chestnut Lodge; Clinical Center, NIH

LAB/BRANCH
Clinical Neurogenetics Branch

SECTION
Section on Clinical Genetics

INSTITUTE AND LOCATION
NIMH, Bethesda, MD 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 2.2 | 1.4 | 0.8 |

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

A study of clinical variables in multiplex families with schizophrenia was completed. In 53 of these families at least 2 siblings satisfied Research Diagnostic Criteria (RDC) for schizophrenia.

Brain imaging study: preliminary analysis of Magnetic Resonance Imaging (MRI) scans of these siblings revealed signficantly reduced hippocampal area in schizophrenics as compared with related controls, suggesting that this may be a familial vulnerability factor.

Genetic marker studies: no association of Restriction Fragment Length Polymorphisms were found in genomic DNA from schizophrenics using several neuropeptide probes and probes for chromosome 11 (see Z01 MH 02237-03 CNG).

Protein polymorphisms in CSF were examined in 14 unrelated schizophrenics with a family history of schizophrenia. No abnormalities were found.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02237-03 CNG

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Molecular Genetics of Neuropsychiatric Disorders

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| P.I.: | S. Detera-Wadleigh | Senior Staff Fellow | CNG, NIMH |
| Others: | E.S. Gershon | Chief | CNG, NIMH |
| | C. de Miguel | Visiting Fellow | CNG, NIMH |
| | B. SenGupta | Guest Researcher | CNG, NIMH |
| | W.H. Berrettini | Staff Psychiatrist | CNG, NIMH |
| | L.E. DeLisi | Staff Psychiatrist | CNG, NIMH |
| | L.R. Goldin | Senior Staff Fellow | CNG, NIMH |

COOPERATING UNITS *(if any)*

Howard University

LAB/BRANCH

Clinical Neurogenetics Branch

SECTION

Section on Clinical Genetics

INSTITUTE AND LOCATION

NIMH, Bethesda, MD 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 4.2 | 2.3 | 1.9 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Genetic linkage of affective disorders (AD) to c-Harvey-ras-1 (HRAS 1) and in insulin (INS) genes on chromosome 11 was examined using three pedigrees with bipolar illness. Our results indicate the absence of linkage from 0 to 15% recombination which contrasts with the finding of another group who found linkage to these markers in a large Old Order Amish pedigree. The reason for this discrepancy is not clear. Conceivably these contrasting findings favor etiological heterogeneity in AD.

Linkage to the color-blindness region, Xq28, was found to be absent in these same pedigrees using the St14 probe.

New restriction fragment polymorphisms (RFLP's) were detected at the gene regions encoding the gastrin releasing peptide (GRP), substance P, muscarinic receptor M-1, muscarinic receptor, M-4 and beta-adrenergic receptor. Analysis of the linkage relationships between AD and these genes are in progress.

New full length calmodulin cDNA for both human and rat have been isolated and sequenced. The nucleotide structures of these cDNAs are substantially different from those that have been reported. These results provide evidence for the presence of at least two actively transcribed calmodulin genes in these species.

A cDNA clone specific for the 87 kDa substrate of protein kinase C (PKCS-87) has been isolated from a rat brain expression library using a polyclonal antibody.

|  |  |
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| DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE<br>NOTICE OF INTRAMURAL RESEARCH PROJECT | PROJECT NUMBER<br>Z01 MH 00935-20 CNG |

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Studies of Plasmids and Small Genomes in Human Cells

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

|  |  |  |  |
|---|---|---|---|
| PI: | C.R.Merril | Chief, Biochemical Genetics Section | CNG, NIMH |
| Others: | L. Mitchell | Staff Fellow | CNG, NIMH |
|  | D. Rath | Staff Biologist | CNG, NIMH |
|  | B. Budowle | Chief, Forensic Sci. Research | FBI,Academy |

COOPERATING UNITS *(if any)*

Forensic Science Research Group, FBI Academy, Quantico, Virginia

LAB/BRANCH

Clinical Neurogenetics Branch

SECTION

Biochemical Genetics Section

INSTITUTE AND LOCATION

NIMH, Bethesda, MD 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 2.25 | 1.25 | 1 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Numerous studies of the human mitochondrial genome have proven the utility of this small, naturally occurring plasmid in elucidating the relationship between populations. The unique perspective provided by investigations of this genome depend on the maternal inheritance pattern of this plasmid and its relatively high rate of mutation. These characteristics of the mit-genome have suggested that it may be useful in identifying individuals and in providing information on the geographic origin of the individuals maternal ancestors. A collaborative study is underway with the FBI Forensic Science Research Group to determine the feasibility of employing the mitochondrial genome in forensic applications. The methods that are being developed in this collaborative study are also being used to examine the rate of mutation of the mit-genome in post-mitotic tissues, such as the central nervous system. Additionally, these methodologies are being used to study a group of diseases that display non-Mendelian maternal inheritance patterns, which may be due to mutational events in the mitochondrial genome.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00941-07 CNG

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Biochemical Genetics and metabolic diseases.

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | C.R.Merril | Chief, Biochemical Genetics Sect. | CNG, NIMH |
| Others: | M.G.Harrington | Visiting Associate | CNG, NIMH |
| | S.Charya | Staff Associate | CNG, NIMH |

COOPERATING UNITS *(if any)* NIMH, NINCDS, USUHS, Vanderbilt University, Harvard Medical School, California Institute of Technology, Baylor College of Medicine, University of Goteborg Sweden, US NAMRU-11 (Philippines).

LAB/BRANCH

Clinical Neurogenetics Branch

SECTION

Biochemical Genetics Section

INSTITUTE AND LOCATION

NIMH, Bethesda, MD 20892

| | | |
|---|---|---|
| TOTAL MAN-YEARS:<br>3.5 | PROFESSIONAL:<br>2.5 | OTHER:<br>1 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Disease-associated cerebrospinal fluid (CSF) protein changes that were previously identified by this group have been further investigated: The presence of two 30,000 MW proteins in CSF of Creutzfeldt-Jakob disease (CJD) patients have been studied prospectively for their usefulness in the diagnosis of 70 nationally and internationally referred cases: no false positives or false negatives were found in the 30 cases that have so far come to autopsy (this has included 3 cases of in-vivo diagnosis of growth hormone transmitted CJD). Further characterization of abnormal CSF proteins have led to purification of 8 proteins for structural analysis, and one of these, a glycoprotein, has been partially sequenced. Four peptide fragments, obtained from a tryptic acid digest, 8 to 18 amino acids in length have been sequenced from this protein. These sequences represent a new protein that has not previously been characterized in the protein sequence data banks. This glycoprotein has been shown to be quantitatively altered in schizophrenia, Parkinson's Disease and multiple sclerosis.

Two dimensional electrophoretic survey studies of brain have been initiated with inbred strains of mice, with a view to developing a protein reference map for both genetic murine disorders and human brain disorders. Similar studies have led to the observation of protein alterations in learning mutants of Drosophila, and T lymphocytes infected with the human immunodeficiency virus.

Continued efforts to investigate protein detection methods has permitted us to develop a physical explanation for the production of specific colors by protein stained with certain silver stains. Electron microscopic studies coupled with computerized image analysis provided evidence that the colors are formed by light scattering which is caused by the presence of silver grains of specific sizes in the gel. Silver grains in yellow bands had an average size of 29.6nm while those in blue bands were 71.6nm in diameter.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

**NOTICE OF INTRAMURAL RESEARCH PROJECT**

PROJECT NUMBER

Z01 MH 01836-09 NS

PERIOD COVERED
October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
GABA/Receptors in the Central Nervous System: Biochemistry to Behavior

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*
PI: S.M. Paul, Chief, NS, NIMH

| | | | |
|---|---|---|---|
| Others: | J. Crawley | Sr Staff Fellow | NS, NIMH |
| | S. Cottingham | PRAT Fellow/Guest Researcher | NS, NIMH |
| | P. Montpied | Visiting Fellow | NS, NIMH |
| | A. Lingford-Hughes | Visiting Fellow | NS, NIMH |
| | P. Suzdak | PRAT Fellow | NIGMS, NIMH |
| | A. Morrow | PRAT Fellow | NIGMS, NIMH |
| | S. Deutsch | PRAT Fellow | NIGMS, NIMH |

COOPERATING UNITS *(if any)*
Laboratory of Bioorganic Chemistry, NIADDK; Section on Molecular Pharmacology, NS, NIMH; Unit on Molecular Neurogenetics, NS, NIMH; Pharmacology Research Associate Training Program, NIGMS; LSU School of Medicine, New Orleans, LA

LAB/BRANCH
Clinical Neuroscience Branch

SECTION
Section on Preclinical Studies

INSTITUTE AND LOCATION
NIMH, NIH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 4.0 | 3.5 | 0.5 |

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Benzodiazepines interact with a specific neuronal membrane receptor to initiate a series of neuronal events resulting in an enhancement of GABA-mediated chloride permeability. The latter results behaviorally in the major pharmacological actions of benzodiazepines, namely their anxiolytic, anticonvulsant, hypnotic and muscle relaxant actions. In addition to benzodiazepines, a variety of sedative/hypnotic agents of the minor tranquilizer class (e.g. the barbiturates) appear to interact with one or more components of the benzodiazepine/GABA receptor complex, and thus the latter has been proposed as a common site of minor tranquilizer action. Several aspects of the benzodiazepine/GABA receptor complex are currently being studies. Recent work has employed an in vitro system for measuring GABA receptor-effector coupling in a subcellular preparation from rat brain (the synaptoneurosome). This technique has greatly facilitated studies on the regulation of the GABA receptor-coupled chloride ion channel. Using this method, we have studied the interaction of ethanol with the GABA receptor complex and have found that ethanol, related short-chain alcohols and several anesthetic agents are capable of stimulating this receptor and at pharmacologically-relevant concentrations. In related studies we have identified a novel imidazobenzodiazepine, Ro15-4513, which blocks both the in vitro effects of ethanol on GABA receptor-mediated $^{36}Cl^-$ uptake as well as many of the behavioral effects of ethanol. Chronic administration of ethanol to rats results in a decrease in GABA receptor-mediated $^{36}Cl^-$ uptake in synaptoneurosomes, an effect that is reversible since it is not observed after the ethanol withdrawal syndrome. In other studies we have examined the use of the radiolabelled benzodiazepine receptor antagonist Ro15-1788 for measuring benzodiazepine receptors in vivo. Our results have validated the suitability of this technique and have demonstrated significant effects of barbiturates, naturally-occurring steroid hormones, ethanol and "stress" on benzodiazepine receptors in vivo.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

**NOTICE OF INTRAMURAL RESEARCH PROJECT**

PROJECT NUMBER

Z01 MH 02186-05 NS

PERIOD COVERED
October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)* Brain Recognition Sites for Stimulants and Antidepressants: Relationship to Pharmacological Activity

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | S.M. Paul | Chief | NS, NIMH |
| Other: | J.N. Crawley | Senior Staff Fellow | NS, NIMH |
| | E. Lestringant | Visiting Associate | NS, NIMH |
| | G. Muscettola | Visiting Scientist | NS, NIMH |
| | P. Skolnick | Pharmacologist | LBC, NIADDK |

COOPERATING UNITS *(if any)*
Laboratory of Bioorganic Chemistry, NIADDK; Section on Molecular Pharmacology, NS, NIMH

LAB/BRANCH
Clinical Neuroscience Branch

SECTION
Section on Preclinical Studies

INSTITUTE AND LOCATION
NIMH, NIH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 4.0 | 3.5 | 0.5 |

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Recognition sites for a variety of psychotherapeutic drugs have been identified in the central nervous system. Over the past several years we have attempted to identify recognition sites for other common psychotropic drugs including tricyclic antidepressants and the psychomotor stimulants, amphetamine and methylphenidate. In each case saturable, and stereospecific binding sites have been delineated; and for amphetamine and methylphenidate relatively good correlations have been observed between the affinities of a series of analogues *in vitro* and at least some of the pharmacological properties of these agents. Recent work has shown that the [3H] (+)-amphetamine binding site in hypothalamic membranes is sensitive to circulating levels of blood glucose. Hypoglycemia decreases, and hyperglycemia increases, the number of [3H](+)-amphetamine binding sites in hypothalamic membranes respectively. Furthermore, these changes seemed to be coupled to th# activity of (Na+ K+) (ATPase; and there is a good correlation between the changes in [3H](+)-amphetamine and [3H]-ouabain binding both *in vivo* and *in vitro*. More recent studies have shown that [3H]-mazindol a chemically unrelated anorectic/psychostimulant also can be used to label the [#H] (+)-amphetamine cognition site and that there is a good correlation between the inhibition of [3H]-mazindol binding by a series of phenylethylamines and their anorectic otencies in rats. These data suggest the existence of a membrane-bound receptor complex capable of "sensing" circulating glucose concentration and in regulating both glucostatic ingestive behavior and perhaps some aspects of the central regulation of energy metabolism. Recent work has demonstrated that genetically obese mice (ob/ob) have an abnormali#y in this system and fail respond to glucoprivic feeding signals. Over the past year, we have developed a method for measuring oubain-sensitivew $^{86}$Rb uptake into synaptoneurosomes and have used this method to measure "sodium pump" activity after treatment with anorectic drugs and in genetically obese rodents.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

**NOTICE OF INTRAMURAL RESEARCH PROJECT**

PROJECT NUMBER

Z01 MH 02340-02 NS

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)* Biochemical and Clinical Studies of Gaucher Disease and Other Neurogenetic Disorders

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: E.I. Ginns, Head, Molecular Neurogenetics Unit, NS, NIMH

| | | | |
|---|---|---|---|
| Others: | W. Eliason | Guest Researcher | NS, NIMH |
| | M. LaMarca | Guest Researcher | NS, NIMH |
| | B. Martin | Visiting Scientist | NS, NIMH |
| | B. Martin | Guest Researcher | NS, NIMH |
| | K. Maysak | Guest Researcher | NS, NIMH |
| | B. Stubblefield | Biologist | NS, NIMH |
| | S. Winfield | Microbiologist | NS, NIMH |

COOPERATING UNITS *(if any)*

Human Genetics Branch, National Institute of Child Health and Human Development; Interinstitute Genetics Program, NIH; Arthritis Service, Hospital for Joint Diseases, New York, NY

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Molecular Neurogenetics Unit, Preclinical Studies Section

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 2.6 | 0.7 | 1.9 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☒ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The clinical study of neurogenetic diseases provides the foundation for the development of techniques for improved diagnosis and strategies for therapy. This goal is greatly facilitated by having a comprehensive knowledge of the biochemistry and clinical heterogeneity of the disorder. Gaucher disease, the most common sphingolipidosis, has a high priority as a model for gaining insight into this group of neurogenetic disorders because of the occurrence of both neuronopathic and non-neuronopathic phenotypes as well as the broad spectrum of clinical diversity within the major types of the disorder. Once the pathophysiologic mechanisms of systemic involvement are understood, the therapy of nervous system dysfunction may be more rationally approached. Basic research on glucocerebrosidase, the enzyme deficient in Gaucher disease, has generated a more detailed understanding of the structure, biosynthesis, intracellular routing, and turnover of the enzyme. These studies will complement other studies within our branch focusing on the investigation of the potential and efficacy of gene transfer as a therapeutic approach. The use of recombinant DNA technologies to produce large amounts of both normal and mutant human proteins is being pursued.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

**NOTICE OF INTRAMURAL RESEARCH PROJECT**

PROJECT NUMBER

Z01 MH 02341-02 NS

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Correction of Inherited Enzyme Deficiencies by Gene Transfer

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: E.I. Ginns, Head, Molecular Neurogenetics Unit, NS, NIMH

| | | | |
|---|---|---|---|
| Others: | B. Martin | Visiting Scientist | NS, NIMH |
| | S. Tsuji | Visiting Fellow | NS, NIMH |
| | B. Stubblefield | Biologist | NS, NIMH |
| | M. LaMarca | Guest Researcher | NS, NIMH |
| | S. Winfield | Microbiologist | NS, NIMH |
| | B. Martin | Guest Researcher | NS, NIMH |
| | W. Eliason | Guest Researcher | NS, NIMH |

COOPERATING UNITS *(if any)*

Center for Cancer Research, MIT and Whitehead Institute for Biomedical Research, Boston, MA

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Molecular Neurogenetics Unit, Preclinical Studies Section

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1.8 | 0.7 | 1.1 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The isolation and characterization of proteins involved in the pathogenesis of neurogenetic disorders has permitted the isolation of cDNA and genomic DNA that can be used to investigate the correction of inherited enzyme deficiencies using recombinant DNA techniques. specifically somatic cell gene transfer. Particularly suited for initial attempts at gene therapy are those disorders (such as Gaucher disease, the most common sphingolipidosis) in which the manifestations of the disorder are due to abnormalities of hematopoietic cells, in this case, the macrophage. In this instance the transfer of normal genes to bone marrow progenitor cells is a rationale therapeutic approach. Using the lysosomal disorder Gaucher disease as a model, we have been successful in utilizing retroviral vectors to transfer and express human glucocerebrosidase in host mouse and Gaucher cell lines. The complete correction of glucocerebrosidase activity in Type 2 Gaucher fibroblasts in culture has provided the impetus for evaluation of retroviral mediated somatic cell gene transfer of the glucocerebrosidase gene into mice by bone marrow transplantation. The initial goal of this research is the application of these recombinant DNA therapeutic strategies to the non-neuronopathic phenotypes. When our understanding of the pathogenetic mechanisms of inherited neurological and psychiatric diseases improves and when retroviral-mediated expression of genes in specific tissues and cells become more predictable, we can begin to investigate the potential usefulness of gene therapy for treatment of selected nervous system disorders.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02342-02 NS

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Gene Regulation within the Nervous System

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: E.I. Ginns, Head, Molecular Neurogenetics Unit, NS, NIMH

| | | | |
|---|---|---|---|
| Others: | B. Martin | Visiting Scientist | NS, NIMH |
| | S. Tsuji | Visiting Fellow | NS, NIMH |
| | S. Winfield | Microbiologist | NS, NIMH |
| | P. Marangos | Unit on Neurochemistry | BPB, NIMH |
| | D. Schmeckel | Neurology Department | VAMC |
| | J. Polak | Royal Post-Graduate Medical School, London | |
| | J. Hozier | Medical Genetics | FIT |

COOPERATING UNITS *(if any)*

Unit on Neurochemistry, Biological Psychiatry Branch, NIMH; Veterans Administration Medical Center, Durham, NC; Royal Post-Graduate Medicl School, London, England; Florida Institute of Technology, Melbourne, FL

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Molecular Neurogenetics Unit, Preclinical Studies Section

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 0.8 | 0.4 | 0.4 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

We approached the cell-specific and developmentally regulated expression of proteins within the nervous system using the neuron specific (NSE) and non-neuronal (NNE) enolase isozymes as a model. Human brain cDNA and genomic DNA libraries were constructed so that the genes for these and other brain specific proteins could be isolated and characterized. Using both antibodies and oligonucleotide probes, cDNAs for both human NSE and NNE have been isolated and sequenced. Employing unique regions of these cDNA clones as probes, the developmentally and cell-specific regulated appearance of mRNA for each of these proteins can be investigated using in-situ hydridization. The human chromosome loci for each of these isozymes will be identified. In addition, the isolation of human genomic clones for each of these proteins should provide information on the regulation of expression of neuron and glial specific proteins during cell differentiation of the human nervous system in normal and disease states. The normal specificity of NSE for neural derived cell lines and the availability of specific DNA probes for NSE should provide a useful approach to the characterization of neural derived normal and tumor cell lineages.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

**NOTICE OF INTRAMURAL RESEARCH PROJECT**

PROJECT NUMBER

Z01 MH 02343-02 NS

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Molecular Genetics of Inherited Neurologic and Psychiatric Disorders

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: E.I. Ginns, Head, Molecular Neurogenetics Unit, NS, NIMH

| | | | |
|---|---|---|---|
| Others: | S.M. Paul | Chief, Clinical Neuroscience Branch | NS, NIMH |
| | D. Pickar | Chief, Section on Clinical Studies | NS, NIMH |
| | J. Kelsoe | Medical Staff Fellow | NS, NIMH |
| | B. Martin | Visiting Scientist | NS, NIMH |
| | B. Stubblefield | Biologist | NS, NIMH |
| | S. Winfield | Microbiologist | NS, NIMH |

COOPERATING UNITS *(if any)*

Pediatrics Department, Johns Hopkins School of Medicine, Baltimore, MD; Florida Institute of Technology, Melbourne, FL; Dept of Anatomy & Neurobiology, Washington Univ School of Medicine

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Molecular Neurogenetics Unit, Preclinical Studies Section

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1.8 | 0.9 | 0.9 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

We approached the characterization of the mutations responsible for inherited neurological or psychiatric disorders by studying the gene organization of specific proteins that might have a role in the pathogenesis of the clinical manifestations. Using the inherited lysosomal storage disorders, Gaucher disease and Fabry disease, as models, we demonstrated that the phenotypic heterogeneity seen within these inherited disorders is a consequence of different mutations, each affecting protein activity and influencing the processing, compartmentalization and/or stability of the protein. Similar approaches are being used to investigate the involvement of genes on chromosome II in mania-depression and other psychiatric disorders. Recombinant DNA techniques have been used to elucidate the structure of the gene for the proteins (enzymes and receptors) involved in these and other neuropsychiatric disorders. Restriction fragment length polymorphisms (RFLPs) have been identified that are useful for the identification of mutations in Gaucher disease that frequently occur in both non-neuronopathic and neuronopathic phenotypes. Northern blot analysis provides further details of the structure of the normal and mutant genes. The molecular mechanisms leading to nervous system involvement in these disorders have also been investigated. The results of this research should provide a more rational foundation for the diagnosis and formulation of therapeutic strategies for these inherited disorders. Genes on chromosome 11 specific for neurotransmitter biosynthesis have been isolated (for example, human tyrosine hydroxylase and tryptophan hydroxylase). Comparison of normal gene sequence to the gene sequence in Amish manic-depressive patients is in progress. Recombinant DNA approaches have been used to produce large amounts of tyrosine hydroxylase isozyme for structural and biochemical studies.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

**NOTICE OF INTRAMURAL RESEARCH PROJECT**

PROJECT NUMBER
Z01 MH 02344-02 NS

PERIOD COVERED
October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Neuropsychiatric Disorders: Protein Structure-Activity Studies

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: B. Martin, Visiting Scientist, NS, NIMH

| | | | |
|---|---|---|---|
| Others: | E.I. Ginns | Head, Molecular Neurogenetics Unit | NS, NIMH |
| | W. Eliason | Guest Researcher | NS, NIMH |
| | K. Maysak | Guest Researcher | NS, NIMH |
| | L. Possani | Free University of Mexico, Mexico | |

COOPERATING UNITS *(if any)*
Free University of Mexico, Mexico

LAB/BRANCH
Clinical Neuroscience Branch

SECTION
Molecular Neurogenetics Unit, Preclinical Studies Section

INSTITUTE AND LOCATION
NIMH, NIH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1.6 | 0.5 | 1.1 |

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This research is part of an effort to better understand the molecular mechanisms underlying human nervous system development and function, as well as the pathogenesis of certain neurogenetic disorders. Our studies have focused on structural and active site properties of the human non-neuronal and neuron specific enolases, lysosomal hydrolase (glucocerebrosidase and alpha-galactosidase A), other enzymes (particularly those peptides and proteins that interact with excitable membranes), and venom toxins. Proteins are purified from both human and animal tissues using affinity chromatography, electrophoretic separation, and high performance liquid chromatography. Using microsequencing techniques, the complete amino acid sequence of glucocerebrosidase, antralin and major portions of sequences for the neuronal and non-neuronal enolases, venom toxins, and alpha-galactosidase A have been obtained. Peptide maps of both normal and mutant proteins are generated using chemical (cyanogen bromide) and enzymatic (trypsin, thermolysin, V8 protease) cleavage. The identification of carbohydrate attachment sites, sulfhydryl residues, and intra-chain disulfide residues is used to predict protein structure. Alkylating agents and enzyme inhibitors are used to define active sites. From the primary protein sequence, hydrophobic and hydrophilic domains of the protein are identified.

Information obtained from these protein structure studies permits the design of oligonucleotides and peptides that are synthesized for collaborative research (see Z01 MH 02343-02 NS) involving antibody production, cDNA cloning, DNA sequence analysis and in vitro mutagenesis.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

## NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 MH 00112-10 NS

PERIOD COVERED
October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Endorphin Research in Mental Illness

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*
PI: D. Pickar, Chief, Section on Clinical Studies NS, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

SECTION

INSTITUTE AND LOCATION

| | | |
|---|---|---|
| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*
INCORPORATED UNDER PROJECTS Z01 MH 02181-05 NS AND Z01 MH 02184-05 NS IN 1987

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

**NOTICE OF INTRAMURAL RESEARCH PROJECT**

PROJECT NUMBER

Z01 MH 02181-05 NS

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Neurobiology of Schizophrenia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: D. Pickar Chief, Section on Clinical Studies NS, NIMH

| | | | |
|---|---|---|---|
| Others: | S.M. Paul | Chief | NS, NIMH |
| | A.F. Breier | Medical Staff Fellow | NS, NIMH |
| | J.R. Kelsoe | Medical Staff Fellow | NS, NIMH |
| | P.B. Lucas | NRSA Fellow | NS, NIMH |
| | C.N. Pato | NRSA Fellow | NS, NIMH |
| | M.H. Rapaport | Medical Staff Fellow | NS, NIMH |
| | J.L. Schreiber | Social Worker | NS, NIMH |

COOPERATING UNITS *(if any)*

Laboratory of Psychology and Psychopathology, NIMH; Neuropsychiatry Branch, St. Elizabeths Hospital, NIMH

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Section on Clinical Studies

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 7.0 | 5.0 | 2.0 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project studies the psychobiology of schizophrenia and attempts to develop improved strategies for its treatment. An important goal is the understanding of the mechanism of action of neuroleptic drugs. We have observed that neuroleptic-induced time-dependent decrease in levels of plasma homovanillic acid (HVA), a major dopamine metabolite, correlates with antipsychotic drug response, suggesting that slow to develop changes in dopamine turnover may underlie the antipsychotic action of neuroleptics. This clinically relevant dopamine marker is further studied using a strategy in which peripherally derived HVA is reduced by the administration of debrisoquin, a MAO inhibitor which does not enter the CNS. In a double-blind, treatment trial, we have observed significant reduction in psychosis in some patients when alprazolam is added to neuroleptic treatment; the use of benzodiazepines to augment neuroleptic response is under investigation in outpatient trials. These data contrast with the negative results found when the calcium channel blocker, verapamil, was administered to neuroleptic-free schizophrenic patients. In a recently completed study using magnetic resonance imaging (MRI) performed in collaboration with the Clinical Brain Disorders Branch, NIMH, compelling evidence was gained which supports enlargement of lateral and 3rd ventricular volumes in schizophrenic patients. A follow-up study of previous inpatients from our program has recently been completed and holds promise for delineating biological correlates of outcome in schizophrenia. A controlled study of expressed emotion in families of schizophrenic patients is in progress. The proposed course involves the further development of an outpatient research program which includes controlled pharmacologic treatment studies and the evaluation of family schizophrenia pedigrees for collaboration with the Clinical Neuroscience Molecular Biology Laboratory. Collaboration with the NIMH positron emission tomography (PET) program focusing on the mechanism of action of typical and atypical neuroleptics using glucose utilization studies and the development of new PET ligands will be pursued.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

**NOTICE OF INTRAMURAL RESEARCH PROJECT**

PROJECT NUMBER

Z01 MH 02184-05 NS

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Neurobiology of Depression

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: D. Pickar, Chief, Section on Clinical Studies NS, NIMH

| | | | |
|---|---|---|---|
| Others: | S.M. Paul | Chief | NS, NIMH |
| | A.F. Breier | Medical Staff Fellow | NS, NIMH |
| | C.N. Pato | NRSA Fellow | NS, NIMH |
| | M.H. Rapaport | Medical Staff Fellow | NS, NIMH |
| | O.M. Wolkowitz | Medical Staff Fellow | NS, NIMH |
| | G.A. Roy | Visiting Associate | LCS, NIAAA |

COOPERATING UNITS *(if any)*

Laboratory of Clinical Studies, NIAAA; Laboratory of Clinical Science, Biological Psychiatry Branch and Laboratory of Neurochemistry, NIMH

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Section on Clinical Studies

NSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 5.0 | 3.5 | 1.5 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The aim of this study is to investigate selected areas of the neurobiology of depression and mania. In previous studies, we have observed that abnormality of noradrenergic and HPA axis dysfunction occur together in seriously depressed patients. We have pursued the study of the role of corticosteroids in depressive illness by examining the effect of exogenous steroid administration. We have found that orally administered dexamethasone produces selective effects on catecholamine function in depressed patients; in contrast to normal controls, depressed patients, particularly those with psychotic features, showed a significant dexamethasone-induced increase in plasma MHPG and a decrease in plasma HVA. These data suggesting abnormal corticosteroid-catecholamine interactions in depression are consistent with the possibility that hypercortisolemia itself may produce or enhance some of the biochemical changes and/or behavioral signs of depression. In a double-blind study of orally administered prednisone (80 mg/day x 5 days) to normal volunteers, we have further investigated steroid effects on the central nervous system. The relationship between stress, steroids, and mood, has been pursued in an experiment in which identical amounts of escapable and inescapable aversive noise stimuli are presented to subjects. Preliminary results suggest that inescapable but not escapable "stress" produces correlated mood and neuroendocrine response. We have examined the effects of permanent separation from one or both biological parent(s) between the ages of 2 and 17 years on the development of adult psychopathology and observed that poorer quality of home life and personal adaptation subsequent to parental loss was associated with significantly higher incidence of major depression as adults and increased levels of plasma cortisol at the time of cross-sectional study. We are currently investigating the therapeutic and biochemical effects of verapamil, a calcium channel antagonist, in manic and hypomanic patients.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

## NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02187-04 NS

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Diazepam Infusions as a Measure of Benzodiazepine Receptor Sensitivity in Humans

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

|  |  |  |  |
|---|---|---|---|
| PI: | D.W. Hommer | Staff Psychiatrist | NS, NIMH |
| Others: | S.M. Paul | Chief | NS, NIMH |
|  | D. Pickar | Chief, Section on Clinical Studies | NS, NIMH |
|  | A. Breier | Medical Staff Fellow | NS, NIMH |
|  | H. Weingartner | Chief, Section on Psychopathology | LPP, NIMH |

COOPERATING UNITS *(if any)*

Laboratory of Psychology and Psychopathology, NIMH; Alcohol Intramural Research Program, National Institute of Alcohol Abuse and Alcoholism; Tufts University

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Section on Clinical Studies

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20205

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1.5 | 1.0 | 0.5 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Increasing doses of the benzodiazepine, diazepam, or placebo were administered to normal volunteers, drug-free alcoholic inpatients. In one series of experiments, subjects were pretreated with either placebo or the benzodiazepine antagonist, Ro-15-1788. Following each dose of drug saccadic eye velocity, diazepam blood levels, plasma cortisol, and growth hormone were measured and self-ratings of anxiety and sedation were performed. After every other dose cognitive testing of memory and attention was performed. The effects of diazepam on these variables was quantified and diazepam dose response curves constructed. These dose response curves provide a measure of benzodiazepine receptor sensitivity in humans, as well as an evaluation of the ability of specific antagonists to block the actions of benzodiazepines.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02188-03 NS

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Biological Studies of Borderline Personality Disorder

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | D.L. Gardner | Staff Psychiatrist | OCD, NIMH |
| Others: | R.W. Cowdry | Clinical Director | NIMH |
| | K.M. O'Leary | Social Worker (Research) | OCD, DIRP, NIMH |
| | D. Pickar | Chief, Sec. on Clinical Studies | NS, NIMH |
| | P. Lucas | Clinical Fellow, NRSA Fellow | NS, NIMH |
| | D.L. Murphy | Chief | LCS, NIMH |

COOPERATING UNITS *(if any)*

Office of the Director, Division of Intramural Research Program, NIMH; Biological Psychiatry Branch, NIMH; Laboratory of Clinical Science, NIMH

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Section on Clinical Studies

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

| | | |
|---|---|---|
| TOTAL MAN-YEARS: 1.7 | PROFESSIONAL: 1.5 | OTHER: 0.2 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project has been transferred to Office of the Clinical Director (OCD).

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| | |
|---|---|
| **DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE**<br>**NOTICE OF INTRAMURAL RESEARCH PROJECT** | PROJECT NUMBER<br>Z01 MH 00179-06 NS |

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Morphological Aspects of Peptides in Mammalian Brain

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | L. Skirboll | Sr. Staff Fellow | NS, NIMH |

COOPERATING UNITS *(if any)*

LAB/BRANCH
Clinical Neuroscience Branch

SECTION
Unit on Electrophysiology, Section on Molecular Pharmacology

INSTITUTE AND LOCATION
NIMH, Bethesda, Maryland 20892

| | | |
|---|---|---|
| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*
PROJECT HAS BEEN DISCONTINUED DUE TO PRINCIPAL INVESTIGATOR'S REASSIGNMENT.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

**NOTICE OF INTRAMURAL RESEARCH PROJECT**

PROJECT NUMBER

Z01 MH 02177-05 NS

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Behavioral Functions of Neuropeptides

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | J.N. Crawley | Senior Staff Fellow | NS, NIMH |
| Others: | L.R. Skirboll | Senior Staff Fellow | NS, NIMH |
| | D.W. Hommer | Staff Psychiatrist | NS, NIMH |
| | J. Mastropaolo | Staff Fellow | NS, NIMH |
| | S.M. Paul | Chief | NS, NIMH |
| | D.M. Jacobowitz | Section Chief | LCS NIMH |

COOPERATING UNITS *(if any)* Unit on Electrophysiology, Section on Molecular Pharmacology, NS and Section on Histopharmacology, Laboratory of Clinical Science, NIMH

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Section on Molecular Pharmacology

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 3.0 | 2.0 | 1.0 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The past decade has witnessed the discovery of forty or more peptides localized in neurons of mammalian brain. Many cases of peptides coexisting in the same neuron with classical transmitters have been described. Our laboratory is investigating the functional significance of coexisting peptides and transmitters in the central nervous system, using behavioral tools.

A) We previously showed that cholecystokinin (CCK) potentiates dopamine-induced hyperlocomotion in the nucleus accumbens, the terminal region of the mesolimbic pathway where CCK and DA coexist. This year, we began to characterize the role of CCK on DA autoreceptors in the ventral tegmentum (VTA), the cell body region of the mesolimbic pathway where CCK and DA coexist. Preliminary data show that CCK potentiates the hypolocomotion induced by DA in the VTA, while having no effect alone, i.e. the potentiating effect of CCK in the VTA was not blocked by doses of proglumide which blocked the potentiating effect of CCK in the nucleus accumbens. In addition, the unsulfated form of CCK-8 was also active in potentiating DA-induced hypolocomotion in the VTA. These preliminary behavioral data suggest that the pharmacology of CCK effects in the VTA match the "central-type" CCK-receptor, as found by Skirboll and Hommer using electrophysiological techniques. Conversely, the pharmacology of CCK effects in the nucleus accumbens match the "peripheral-type" CCK receptor in our previous behavioral data.

B) The nucleus basalis of Meynert lesion rat model of Alzeheimer's disease is now ongoing in our laboratory. We have completed one experiment showing that acetylcholine (ACH) can reverse the memory deficit in a T-maze task when given directly into the lateral ventricles, the first demonstration of a central site of action for ACH. The second experiment found that atropine, but not mecamylamine, blocked the ACH effect, suggesting the involvement of a muscarinic, rather than a nicotinic cholinergic receptor. Tests of somatostatin and galanin, alone and in combination with a submaximal dose of ACH, are in progress.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02178-04 NS

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Pharmacology of Anxiety

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | J.N. Crawley | Senior Staff Fellow | NS, NIMH |
| | R.C. Drugan | NRSA Fellow | NS, NIHM |
| Others: | P. Skolnick | Pharmacologist | LBC, NIADDK |
| | Leslie Morrow | | NS, NIMH |
| | Steve Deutsch | | NS, NIMH |
| | Avi Weizman | | NS, NIMH |
| | Ronit Weizman | | NS, NIMH |
| | Steven M. Paul | Chief | NS, NIMH |

COOPERATING UNITS *(if any)*

Unit on Electrophysiology, Section on Molecular Pharmacology, NS, NIMH; Laboratory on Bioorganic Chemistry, NIADDK.

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Section on Molecular Pharmacology

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1.0 | 1.0 | |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Animal models of anxiety are being used to investigate the biological mechanisms underlying anxiety-related behaviors. The anxiety component of the learned helplessness model of depression was characterized using in vivo binding of $^3$H-Ro15-1788 and in assays of chloride flux in brain regions from rats experiencing escapable versus inescapable stressors.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

**NOTICE OF INTRAMURAL RESEARCH PROJECT**

PROJECT NUMBER

Z01 MH 02179-05 NS

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Animal Models of Neuropsychiatric Disorders

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | J.N. Crawley | Senior Staff Fellow | NS, NIMH |
| Others: | S.M. Paul | Chief | NS, NIMH |
| | P. Suzdak | Staff Fellow | NS, NIMH |
| | G. Wand | Asst. Professor<br>Dept of Neuroscience, Johns Hopkins University School of Medicine | |

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Section on Molecular Pharmacology

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 0.5 | 0.5 | 0 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Characterization of a benzodiazepine, Ro15-4513, which antagonizes the biochemical actions of ethanol in the rat, was performed on the behavioral test for intoxication. Other inverse agonists such as FG-7142 and β-CCE did not block the intoxicating effects of ethanol, suggesting that Ro15-4513 acts through a mechanism which is independent of any direct behavioral effects of inverse agonists of the central benzodiazepine receptor.

Preliminary assays of neuropeptides in the hypothalamus of dwarf hamsters found increased levels of NPY in separated males. Microinjection of NPY in rats is known to stimulate feeding; separated male dwarf hamsters have increased body weight.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

**NOTICE OF INTRAMURAL RESEARCH PROJECT**

PROJECT NUMBER

Z01 MH 02180-05 NS

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)* Electrophysiological Studies of Peptidergic and GABAergic Function in Mammalian Brain.

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | D. Hommer | Staff Psychiatrist | NS, NIMH |
| Others: | L. Skirboll | Sr. Staff Fellow | NS, NIMH |
| | J.N. Crawley | Sr. Staff Fellow | NS, NIMH |
| | S.M. Paul | Chief | NS, NIMH |

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Unit on Electrophysiology, Section on Molecular Pharmacology

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 2.0 | 1.5 | .5 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Using extracellular single unit recording techniques, we have examined the effects of stress and pharmacological agents which either alleviate or mimic the effects of stress on individual neurons in the rat substantia nigra (SN). Specifically, learned helplessness induced by uncontrollable stressful shocks results in a supersensitivity to gamma-amino butyric acid (GABA) agonists while shocks which are controllable do not produce GABAergic supersensitivity. The anxiogenic benzodiazepine (BZ) receptor ligand, beta-carboline carboxylate ethyl ester (βCCE) increases the activity of neurons in the SN zona reticulata (ZR) but had no effect on noradrenergic neurons in the locus coeruleus. Caffeine also mimics many of the effects of βCCE in the SN but its actions are not reversed by the specific BZ antagonist Ro15-1788 as are those of βCCE. Furthermore, the effects of caffeine could be blocked by lesions of the caudate nucleus while the effects of βCCE were unaffected by such lesions.

We have continued our studies on the interactions between endogenously occurring neuropeptides and classical neurotransmitters. All varieties of CCK-like peptides which bind to brain CCK receptors also potentiate DA in those areas where CCK and DA coexist while those CCK-like peptides which do not bind to this receptor are ineffectual in facilitating DA inhibition. The putative cholecystokinin (CCK) antagonists, proglumide and benzotript, were found to weakly block CCK in proportion to their potency at central CCK receptors.

Dynorphin (DYN) appears to modulate the response of SNZR neurons to GABA. Finally, we have examined the effects to cholinergic agents in the SN. Nicotinic agents appear to activate DA neurons in the SN through a central mechanism.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

## NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02182-05 NS

PERIOD COVERED
October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Toward the Visualization of Opiate Receptors in Living Humans

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

| | | | |
|---|---|---|---|
| PI: | C. B. Pert | Guest Researcher | NS, NIMH |
| Others: | N. L. Ostrowski | Senior Staff Fellow | LCM, NIMH |
| | K. C. Rice | Pharmacologist | LC, NIDDK |

COOPERATING UNITS (if any)

Laboratory of Chemistry, NIDDK

LAB/BRANCH
Clinical Neuroscience Branch

SECTION
Section on Brain Biochemistry

INSTITUTE AND LOCATION
NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

| | | |
|---|---|---|
| TOTAL MAN-YEARS: 3.5 | PROFESSIONAL: 2.5 | OTHER: 1.0 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The distribution of positron emitting substances in brain can be followed by positron emission tomography (PET). We are developing $^{18}F$-labeled high affinity opiate drugs to be injected into living humans for the visualization of opiate receptor patterns in vivo. It will be interesting to determine whether opiate receptor distribution patterns in cortex change as a function of attention and emotional states. Meanwhile, we have carefully documented the receptor-binding properties and kinetics of $^{3}H$-cyclofoxy in rat brain after in vivo injection.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

**NOTICE OF INTRAMURAL RESEARCH PROJECT**

PROJECT NUMBER

Z01 MH 02183-05 NS

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Is Schizophrenia an Autoimmune Neuropeptide Receptor Disease?

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | C. B. Pert | Guest Researcher | NS, NIMH |
| Others: | J. G. Knight | Guest Researcher | NS, NIMH |
| | P. Laing | Visiting Associate | NS, NIMH |

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Section on Brain Biochemistry

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 4.0 | 4.0 | |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The notion that schizophrenia has an important autoimmune component has been around for several decades, but has not previously been subjected to analysis by the most sensitive, modern techniques. We have hypothesized that early (perinatal) tolerance to viruses, which use the receptor molecule to gain cellular entry, causes this autoimmunity. We have developed a simple sensitive assay for detecting antibodies directed against human brain found in sera of schizophrenic patients and controls. We are now subjecting human brain membrane receptors to either native or denaturing solubilization conditions and separation by polyacrylamide gel electrophresis (PAGE). After visualization by antiserum or CSF from patients and controls, we hope to identify the specific brain antigens against which schizophrenics have generated antibodies.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

**NOTICE OF INTRAMURAL RESEARCH PROJECT**

PROJECT NUMBER

Z01 MH 02189-04 NS

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Neuropeptides and their Receptors are Shared by the Brain and the Immune System

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | C. B. Pert | Guest Researcher | NS, NIMH |
| Others: | P. Sacerdote | Visiting Fellow | NS, NIMH |
| | J. M. Hill | Senior Staff Fellow | NS, NIMH |
| | M. R. Ruff | Guest Researcher | NS, NIMH |

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Section on Brain Biochemistry

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 4.0 | 2.5 | 1.5 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Neuropeptides, small signal peptides largely known for their role as transmitters of nerve impulses in the brain which mediate mood and emotion, have now been shown to regulate immune system function. Our work reveals that human monocytes have receptors and will respond chemotactically to numerous neuropeptides. Neuropeptides which we have reported on include β-endorphin and other opiates, substance P and bombesin. We have shown that a major class of psychoactive drugs, the benzodiazepines, are also potent chemoattractants. In this case we have directly demonstrated the presence of chemotactic receptors through ligand binding experiments. The presence of diverse, distinct neuropeptide chemotactic receptors on monocytes and other immune system cells suggests the existence of a neuroendocrine link between the brain and the immune system whose purpose is to integrate behavioral and emotional responses with immune system function.

In addition to the presence of neuropeptide receptors we have also been able to demonstrate that human alveolar macrophages store and secrete the neuropeptide bombesin. Neuropeptide synthesis is, therefore, a general feature of various immune cell populations. Such results are consistent with a multi-directional communication network via neuropeptides and their receptors. The purpose of this network is to link the body's cellular defense and repair systems with the nervous and endocrine systems and thereby integrate the internal millieu of the whole organism. The flow of information in this network is perceived by the human organisms emotional and/or altered states of consciousness. Ultimately, this results in behavioral decisions at the whole organism level. Additional work has suggested that a major cause of human cancer, small cell lung carcinoma, may not, as previously thought, arise from lung epithelium but originates from hemopoietic cells when the normal macrophage mediated repair of lung tissue is deranged by continuous heavy smoking.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

**NOTICE OF INTRAMURAL RESEARCH PROJECT**

PROJECT NUMBER

Z01 MH 02190-04 NS

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Distribution and Properties of Opiate and Other Brain Receptors

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | C. B. Pert | Guest Researcher | NS, NIMH |
| Others: | M. R. Ruff | Guest Researcher | NS, NIMH |
| | C. M. Fraser | Pharmacologist | LNP, NINCDS |
| | C. J. Venter | Chief, Recept. Biochem. | LNP, NINCDS |

COOPERATING UNITS *(if any)*

Section on Receptor Biochemistry, Laboratory of Neurophysiology, NINCDS

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Section on Brain Biochemistry

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 4.0 | 2.5 | 1.5 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☑ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Cross-linking is a relatively recent biochemical strategy for covalently affixing reversible ligands to their recognition molecules for subsequent electrophoretic analysis. $[^{125}I]$-Tyr$^{27}$-β-endorphin (prepared as originally described by Smythe and co-workers) binds stereospecifically to rat brain membranes. While some studies have suggested that the β-endorphin receptor is a unique "epsilon" opiate receptor, a larger body of evidence suggest that β-endorphin has high affinity for most if not all of the opiate receptors types and subtypes. Cross-linking opiate receptors from different tissue sources can potentially reveal much information about the molecular basis of apparent opiate receptor heterogeneity. Cross-linking, however, only fixes 1% of the bound trace and SDS-PAGE while exquisitely sensitive, can fail to reveal substantial inter-molecular differences. Cross-linking was performed with the homo bi-functional reagent Disuccinimidyl Suberate (DSS). The iodinated cross-linking products of Tetrahymena, leech CNS, and rat brain membranes (both type 1 and type 2 conditions) appeared indistinguishable on SDS-PAGE gel with major cross-linking products at 58K and 100-110K. The strong cross-linked bands produced by incubation in the presence of the inactive opiate ((+)-naloxone) was completely abolished by the same ($10^{-6}$M) concentration of its active isomer (-)-naloxone. Although we have thus far failed to distinguish between opiate receptors from a mammal, an invertebrate, and a unicellular organism, we continue to explore various conditions of binding, and electrophoresis, (e.g., reduced and unreduced) to examine possible receptor differences, both intra and inter species. Electrophoresis of proteolytic digests of cross-linked bands will be performed as a particularly sensitive method for distinguishing heterogeneity. Thus far, our cross-linking experiment suggest that the recognition molecule (the opiate receptor) which binds all opiate alkaloids and peptides is stable across evolution. As proposed, apparent physiological receptor heterogeneity is due to coupling to other membrane components.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

## NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02191-02 NS

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Brain Receptors for the AIDS Virus and Other Neurotrophic Viruses

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | C. B. Pert | Guest Researcher | NS, NIMH |
| Others: | J. M. Hill | Senior Staff Fellow | NS, NIMH |
| | E. M. Sternberg | Guest Researcher | NS, NIMH |
| | M. R. Ruff | Guest Researcher | NS, NIMH |
| | P. Sacerdote | Visiting Fellow | NS, NIMH |

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Section on Brain Biochemistry

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1.5 | 1.0 | 0.5 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

We have demonstrated that the 60 kD protein previously characterized on a subset of T lymphocytes and named "T4", is another example of shared components between the brain and immune system. Thus, we have demonstrated that this cell surface molecule can be cross-linked to $^{125}$I labeled AIDS virus envelope and immunoprecipitated by the Mab OKT4 in both T cells and brain. Furthermore, we have mapped the brain distribution pattern of the AIDS virus receptor, T4 in monkey, human and rat brain and shown that it is most enriched in areas of the cortex and the hippocampus which subserves cognition and other higher functions. Our work suggest that the neuropsychiatric effects of AIDS may not, as previously thought, be due to inflammatory processes but may be due to a direct neuronal infection of the virus.

We have identified, synthesized, and studied an octapeptide "peptide T", which appears to be the critical attachment area of the AIDS viral envelope. Peptide T and several rationally designed peptide analogs appear to bind with high affinity to the AIDS virus receptor, blocking viral infectivity at very low concentrations. We expect that synthetic peptide heteropolymers employing this core pentapeptide attachment sequence will prove valuable as an approach for a vaccine for AIDS.

This method and approach appears useful for exploring the presence of other virus receptors in brain. For example, we have already observed that the Epstein-Barr virus which has been known to use the complement receptor on B cells as a receptor entry protein, may actually infect brain via the same receptor molecule which we have recently identified in brain.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02152-08 LDP

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Discipline and Parental Control in Families with Affective Disorders

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | G. Kochanska | Research Psychologist | LDP/NIMH |
| Other: | L. Kuczynski | Assoc. Prof. of Psychology | Univ. of Guelph<br>Guelph, Ontario |
| | M. Radke-Yarrow | Chief | LDP/NIMH |

COOPERATING UNITS *(if any)*

University of Guelph
Guelph, Ontario Canada

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| .82 | .35 | .47 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☒ (a1) Minors
- ☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Mothers' discipline and control practices and their children's responses to maternal control attempts are studied in well and clinically depressed mothers. Impaired parental skills in managing children's behavior have often been implied in the etiology of maladaptive patterns of child development. Depressive symptomatology has been linked to inappropriate control practices, but specific difficulties of depressed mothers and possible implications for their children's development have not been identified. Assessments of mother and child behavior are based on observations of their interaction in a naturalistic setting (see Annual Report MH 02144). Detailed measures of maternal control were taken, including goals, timing and specific techniques, and the overall interactive quality of control episodes. Child response was also measured in terms of compliance to maternal demands and in terms of level of social competence of noncompliance strategies. Analyses revealed that affectively ill mothers, compared to well mothers, have specific difficulties controlling their children. In particular, they are more likely to avoid confronting the child and less able to negotiate a compromise after their initial intervention meets with child's resistance. Children of well mothers, but not of depressed mothers, became more cooperative over time. Daughters of depressed mothers appeared at particular risk for noncompliance problems.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 MH 02155-08 LDP

PERIOD COVERED
October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Children of Depressed and Normal Parents

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | C. Zahn-Waxler | Chief, Sec. on Child Behavior Disorders | LDP/NIMH |
| Other: | E. Cummings | Professor | University of West Virginia |
| | R. Iannotti | Research Psychologist | Georgetown University |
| | K. Rubin | Professor | University of Waterloo |
| | S. Denham | Associate Professor | George Mason Univ. |

COOPERATING UNITS *(if any)*
University of West Virginia
University of Waterloo
Georgetown University
George Mason University

LAB/BRANCH
Laboratory of Developmental Psychology

SECTION
Section on Child Behavior Disorders

INSTITUTE AND LOCATION
National Institute of Mental Health, NIH, 9000 Rockville Pike, Bethesda, MD 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| .82 | .40 | .42 |

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☒ (a1) Minors
☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of this study is to identify early in development dimensions of personality and social-emotional functioning that relate to the expression of problem behaviors in children as they reach school age. The focus is on the development of both externalizing (aggression) and internalizing (anxiety and depression) symptoms. Patterns of continuity and discontinuity are examined separately for children from high and low risk environments. Children's emotion expressions and social interactions at age two and age five were observed. A psychiatric assessment was obtained at age six. Significant patterns of continuity in internalizing and externalizing problems have been identified; early problem behaviors observed in children's social interactions predict internalizing and externalizing symptoms at school age. Good social skills in toddlers appear to be protective factors. Further coding and analyses are in progress to assess children's appropriate use of affect in guiding social interactions, their strategies for achieving goals and solving problems in interpersonal situations, and the nature of their dyadic play.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02156-08 LDP

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Personality of Children Reared by Normal and Depressed Mothers: Inhibited Children

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | F. Bridges-Cline | Guest Researcher | LDP/NIMH |
| Other: | G. Kochanska | Research Psychologist | LDP/NIMH |

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| .22 | .10 | .12 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☒ (a1) Minors
  ☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This study focuses on the role of early childhood inhibition in the development of pathological risk indicators in children of families with and without parental depression. Patterns of child behavior in the face of the unfamiliar (persons, places) such as behaviors expressing inhibited exploratory activity and social withdrawal are observed at 2 to 3 years of age in semi-naturalistic but standard settings, which represent varied contexts of unfamiliarity. Analyses of these data revealed that five reliable dimensions of response styles could be empirically derived from our observation coding system. These dimensions meaningfully distinguish groups of children in our sample at this very young age. Comparisons of these five dimensions of early behavioral inhibition across maternal diagnostic groups (normal, major depressive and bipolar) indicate that the young children of the major depressive mothers typically exhibit the most inhibited forms of exploratory behavior, a strong tendency to cling to mother in novel situations, and characteristically flat and withdrawn displays of affect. Children of the bipolar mothers typically exhibit the most active and independent forms of explorations of novel environments. In a situation of an unfamiliar person, these children score at both the inhibited and uninhibited polar extremes. However, in this situation, these children of bipolar mothers do not demonstrate a clinging dependency on mother and typically present positive displays of affect. Observational data relating to mothers' behaviors that are concurrent with child behaviors in these situations are being analyzed to examine the ways in which mothers in these groups function to facilitate or hinder the child's exploration and approach of unfamiliar situations.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02164-07 LDP

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Biological changes and psychological functioning during adolescence

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | E.J. Susman | Guest Researcher | LDP NIMH |
| OTHER: | E.D. Nottelmann | Statistician | LDP NIMH |
| | G.I. Germain | Research Psychologist | LDP NIMH |
| | L.D. Dorn | Guest Researcher | LDP NIMH |
| | G.P. Chrousos | Senior Investigator | DEB NICHD |
| | G.G. Cutler | Senior Investigator | DEB NICHD |
| | D.L. Loriaux | Chief | DEB NICHD |

COOPERATING UNITS *(if any)*

Developmental Endocrinology, NICHD

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| .97 | .75 | .22 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☒ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The interrelations of psychological functioning and endocrine and physical growth factors in young adolescents are investigated. Participants are 56 boys and 52 girls, 9 to 14 years old, and their parents. Participants were evaluated three times, six months apart on (a) stage of pubertal development (Tanner criteria), and hormone levels (serum levels of gonadotropins, gonadal steroids, adrenal androgens, and cortisol), and (b) psychological status (cognitive functioning, moods, problem behavior, competencies, social supports and interactions with parents). Higher levels of adrenal androgens and cortisol and older chronological age predicted higher degrees of self-reported anxiety and depressive symptoms for boys; for girls, these symptoms were predicted by lower levels of gonadotropins. For both sexes, adolescents who reported an absence of psychological support from their parents also reported higher degrees of anxiety and depressive symptoms. In a clinical situation involving a mild stress (blood drawn for hormone assessments), adolescents with higher cortisol levels exhibited higher levels of observed behavioral distress on first exposure to the stressor. This association disappeared when the situation became familiar.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02169-05 LDP

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Interactions Between Siblings With a Depressed Parent

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | C. Zahn-Waxler | Research Psychologist | LDP NIMH |
| OTHER: | D. Hay | Research Psychologist | Univ. of London |
| | M. Radke-Yarrow | Chief | LDP NIMH |

COOPERATING UNITS *(if any)*

Univ. of London

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

Child Behavior Disorders

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| | | |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☒ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project has been incorporated into project Z01 MH 02370.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02170-05 LDP

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Psychiatric Assessment of Infants and Toddlers

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | L. Cytryn | Medical Officer (Psych) | LDP/NIMH |
| Other: | T. Sherman | Research Psychologist | LDP/NIMH |
| | D. McKnew, Jr. | Medical Officer (Psych) | LDP/NIMH |

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

Section on Affective Development

INSTITUTE AND LOCATION

National Institute of Mental Health, NIH, 9000 Rockville Pike, Bethesda, MD 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1.55 | .45 | 1.10 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☒ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

One hundred and twenty-three children, 2 to 3 years of age, were assessed using two structured, behavioral observation systems: in a psychiatric play interview in the absence of mother, (see Z01 MH 02170-03), and in interaction with mother (see Z01 MH 02230-01). Twenty-two mothers had Bipolar Disorder, 45 Major Depressive Disorder, 11 Minor Depressive Disorder, and 45 with no history of psychiatric disorder. All children were assigned a rating (1 to 4) of degree of risk for later development of psychopathology based on their performance in each setting. This produced four groups of children: a low risk group with low risk ratings in both assessments, two mixed-risk groups with ratings of 1 or 2 in one setting, and 3 or 4 in the other, and a high risk group with ratings of 3 or 4 in both assessments. From a case-by-case analysis of the 16 children in the high risk group, three major constellations of behavioral symptoms were discernible: One was seen in a boy from a healthy home who displayed little affect, had a very distant type of relationship with his mother, and would not speak with the psychiatrist in the play session. A second pattern was seen in three girls from relatively poor families in which mother suffered from major depression. This pattern consisted of a distant type of relationship with mother, dysphoria, and anhedonia. The third pattern was seen in the remaining group of twelve children (4 girls and 8 boys). These children came from homes that varied in social class, and diagnostic status of the parents. The behavior consisted of an angry relationship with mother, and predominantly angry mood. The children in all three groups demonstrated dysregulation of emotions under stress, and little or no interest in play.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02171-04 LDP

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Protective and Risk Factors in Childrearing: Contributions of Fathers

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | W.E. Wilson | Guest Researcher | DRG/NIH |
| OTHERS: | J.E. Richters | Staff Fellow | LDP/NIMH |

COOPERATING UNITS *(if any)*

Division of Research Grants, NIH

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| .70 | .25 | .45 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☒ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The husbands of depressed women may buffer their children from the stresses of living with a depressed mother by encouraging dialogue, maintaining stability and equilibrium within the family, and providing children with a supportive environment. But they may also exacerbate the stresses to which their children are exposed by not functioning effectively in these roles.

The objective of the present study is to examine the functioning of spouses by combining measures of psychopathology and deviance in the spouses of depressed women with detailed assessments of their functioning with and around their wives and children. These measures will then be examined for their contributions to predictions of children's adjustment. Analyses will be based on interview, case history, and direct observation data from families participating in a follow-up phase of the NIMH Childrearing Project, which includes children of parents with and without a history of affective disorder.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02207-04 LDP

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

The Affective Rearing Environment: A Comparison of Normal and Depressed Parents

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | M. Radke Yarrow | Chief | LDP NIMH |
| OTHER: | G. Kochanska | Res. Psychologist | LDP NIMH |
| | W.E. Wilson, Jr. | Res. Psychologist | LDP NIMH |
| | L. Kuczynski | Assoc. Professor | U. Of Guelph |
| | E. Nottelmann | Statistician | LDP NIMH |
| | J. Richters | Res. Psychologist | LDP NIMH |
| | B. Belmont | Soc. Sci. Analyst (Clin.) | LDP NIMH |
| | A. Mayfield | Soc. Sci. Analyst | LDP NIMH |
| | J. Stilwell | Res. Nurse Prac. (Psychiatric) | LDP NIMH |

COOPERATING UNITS *(if any)*

Univ. of Guelph, Guelph, Ontario, Canada
Division of Research Grants, NIH

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1.97 | .95 | 1.02 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☒ (a1) Minors
- ☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Affective characteristics of depressed and well mothers are investigated in relation to the affect and behavior of their children. The moods and emotions observed in the parent and experienced in interaction with the parent are significant socialization influences on the child's own affective development. The affective impairments that are characteristic of depression, if manifested by depressed mothers in their interactions with their children, are likely to create unpredictable, noncontingent, and stressful daily experiences for their children. The questions of interest concern the nature of mother's affective profile, the concordances between mother and child's moods and emotions, the relation of affect to other aspects of child development. When mother and child are analyzed as pairs, there is a high degree of concordance in their affective expression regardless of mother's diagnosis or gender of child. Depressed mother-child dyads are most frequently concordant in negative affect. Mutual positive affect between mother and child is significantly diminished in families characterized by disorganization or chaotic life conditions. The mutual positive affect at 2 to 3 years is predictive of the child's ability three years later to relate competently to an unfamiliar peer.

| | |
|---|---|
| DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE<br>NOTICE OF INTRAMURAL RESEARCH PROJECT | PROJECT NUMBER<br>Z01 MH 02229-03 LDP |

PERIOD COVERED
October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Vocalic Analysis of Natural Discourse in Well and Depressed Mothers

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | T. Sherman | Research Psychologist | LDP/NIMH |
| Other: | Z. Breznitz | Assistant Professor | University of Haifa<br>Israel |

COOPERATING UNITS *(if any)*

University of Haifa

LAB/BRANCH
Laboratory of Developmental Psychology

SECTION
Section on Affective Development

INSTITUTE AND LOCATION
National Institute of Mental Health, NIH, 9000 Rockville Pike, Bethesda, MD 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| .72 | .30 | .42 |

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☒ (a1) Minors
☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The speech behavior of 14 depressed and 18 nondepressed mothers during conversation with their 3-year-old children was examined in this study. It was found that (Annual Report #Z01 MH 02229-02 LDP) depressed mothers vocalized less often and responded less quickly to the cessation of their children's speech than healthy mothers. In a mildly stressful situation, (awaiting a doctor's visit), the depressed mothers, but not the healthy mothers, significantly increased their level of speech productivity. Children of the depressed mothers spoke less than children of healthy women, particularly while sitting and eating lunch with their mothers. The observed differences in the mothers' behaviors were interpreted as an indication that the two groups of children are exposed to very different patterns of socialization. The offspring of depressed women are being taught both to keep social interaction to a minimum and to be overreactive to even mild stresses. The differences in the children's behavior may indicate that already these 3-year-old children have learned to keep their interactions with their mother to a minimum. This manner of adaptation may have negative effects on the child's continued social, emotional and cognitive development.

In order to understand the developmental impact of the observed aberrant patterns of vocalic interaction between depressed mothers and their young children, two further studies are underway. First, the question of continuity of experience will be addressed by analyzing the conversation patterns of these women and children three years after the initial observation. Second, the question of alternate environmental supports for the children's development will be examined by assessing the conversation patterns of these young children and their older siblings. These observations are of the children both at the time of the original assessment of mother-child interaction and again at the time of the first follow-up assessment.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

## NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02231-03 LDP

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Biological-Behavioral Relations in Early Adolescence

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | E.D. Nottelmann | Statistician | LDP/NIMH |
| Other: | E.J. Susman | Guest Researcher | LDP/NIMH |
| | G.I. Germain | Research Psychologist | LDP/NIMH |
| | L.D. Dorn | Guest Researcher | LDP/NIMH |
| | G.P. Chrousos | Senior Investigator | DEB/NICHD |
| | G.B. Cutler, Jr. | Senior Investigator | DEB/NICHD |
| | D.L. Loriaux | Chief | DEB/NICHD |

COOPERATING UNITS *(if any)*

Developmental Endocrinology, NICHD

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1.17 | 1.05 | .12 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☒ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Interrelations of pubertal development and adolescent adjustment and behavior are investigated cross-sectionally and longitudinally. Participants are 9- to 14-year-old boys and girls and their parents. The adolescents and their parents are seen three times, six months apart. Measures of pubertal development include serum hormone levels (gonadotropins, sex steroids, and adrenal androgens), pubertal stage (Tanner criteria), and height and weight. Psychological assessments of the adolescent include adolescent- and parent-report of behavior problems and competencies and behavioral observations of parents and their adolescent in family interactions. Comparisons of ratings of pubertal stage made by medical personnel, the adolescents, and their parents indicate that, with appropriate instruction, adolescents and parents can provide valid assessments of the adolescent's pubertal stage. Analyses involving pre- and postmenarchial girls indicate that mean levels of gonadotropins, sex steroids, and adrenal androgens are higher in postmenarchial than premenarchial girls, but that there is considerable overlap in the distributions. Preliminary analyses suggest that there are similar hormone-behavior relations in pre- and postmenarchial girls. An examination of relations between hormone levels and the adolescents' use of anger and power in family interactions indicates that estradiol and androstenedione levels are related to irritability and assertive forms of aggression shown by girls. For both sexes, there was evidence that controlling behaviors shown by parents and anger shown by adolescents are related in a pattern which results in an escalation of conflict.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 MH 02232-03 LDP

PERIOD COVERED
October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Development of Ability to Concentrate in Children of Depressed and Well Mothers

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | Z. Breznitz | Research Psychologist | Univ. of Haifa<br>Haifa, Israel |
| Other: | S.L. Friedman | Health Scientist Administrator | HLB, NICHD |

COOPERATING UNITS *(if any)*
University of Haifa, Haifa, Israel
Human Learning and Behavior Branch, NICHD

LAB/BRANCH
Laboratory of Developmental Psychology

SECTION

INSTITUTE AND LOCATION
National Institute of Mental Health, Bethesda, Maryland 20892

| | | |
|---|---|---|
| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☒ (a1) Minors
☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Both investigators have taken other positions. Further work on the project will be carried on outside the Laboratory.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02233-02 LDP

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

The Development of Guilt: Language, Emotions, and Behavior

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | C. Zahn-Waxler | Chief, Sec. on Child Behavior Disorders | LDP/NIMH |
| Other: | G. Kochanska | Research Psychologist | LDP/NIMH |
| | S. Denham | Associate Professor | George Mason University |

COOPERATING UNITS *(if any)*

George Mason University

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

Section on Child Behavior Disorders

INSTITUTE AND LOCATION

National Institute of Mental Health, NIH, 9000 Rockville Pike, Bethesda, MD 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| .92 | .50 | .42 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☒ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This research focuses on the establishment of methods to investigate the development of guilt in children. Families and children are selected for characteristics (e.g., socioeconomic status, gender, parental depression) that, on theoretical grounds, might be expected to contribute to differential development of guilt and different forms of expression.

Two- to three-year-old children are observed in structured situations in which a problem or mishap occurs. Analyses focus on identification of individual differences in children's reactions. Preliminary results indicate that expressions of guilt and avoidance of responsibility are already present in toddler-age children and take varied functional and dysfunctional forms. Children between 5 and 8 years of age (Z01-MH-02155) are administered a series of pictures of children and adults in circumstances of distress and conflict to tap their propensities for guilt and related affects. In normal control families, children in this age range show the characteristic increases in guilt expected with age, but children with a depressed parent do not. Levels of guilt are lowest in children with parents of low socio-economic status. Guilt scores on this test relate to guilt and anxiety scores in a clinical interview, but only for children with emotionally well parents.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02297-02 LDP

PERIOD COVERED
October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Generosity and Sharing in Children of Normal or Affectively Disturbed Parents

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | F.R. Ascione | Guest Researcher | LDP/NIMH |
| Other: | M. Radke-Yarrow | Chief | LDP/NIMH |
| | C. Zahn-Waxler | Chief, Sec. on Child Behavior Disorders | LDP/NIMH |

COOPERATING UNITS *(if any)*

None

LAB/BRANCH
Laboratory of Developmental Psychology

SECTION
Section on Child Behavior Disorders

INSTITUTE AND LOCATION
National Institute of Mental Health, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| .47 | .05 | .42 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☒ (a1) Minors
- ☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The ability to relate positively to other persons is an important aspect of development. One indicator of this achievement is the child's capacity for empathy and ability to help or share with another person. The purposes of this study are to: (1) examine 5-9 year old children's generosity in a laboratory measure of sharing and also in a naturalistic setting with their younger siblings; and (2) explore proximal and distal correlates of generosity and sharing, and their relation to parental diagnostic status (affectively disturbed or normal). (3) There is also a methodological interest in comparing the standard laboratory measure of sharing that has been the basis of the majority of studies of sharing with measures of sharing in the context of the child's family interactions. This study uses data collected during the first phase of a longitudinal study of child rearing and parental affective disorders.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02361-01 LDP

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Relation between Self- and Teacher-reports of Social-emotional Adjustment

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | T. Sherman | Research Psychologist | LDP/NIMH |
| Other: | D. Pellegrini | Professor | Catholic University |

COOPERATING UNITS *(if any)*

Catholic University

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

Section on Affective Development

INSTITUTE AND LOCATION

National Institute of Mental Health, NIH, 9000 Rockville Pike, Bethesda, MD 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| .52 | .10 | .42 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☒ (a1) Minors
  ☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

One hundred and twenty-three children (the entire group of older siblings in the NIMH Childrearing Study, Annual Report # Z01 MH 0229-01 LDP) 8 - 11 years of age were administerd the Child Assessment Schedule (CAS), a structured psychiatric interview. In addition, the children's teachers filled out the Achenbach Child Behavior Checklist - School Version. The Achenbach asks the teachers to report on the children's ability to relate to other children, the children's behavior, and the children's academic achievement.

The question addressed by this study is the extent to which the children's reports of negative affective states, poor social relationships with family members and/or peers, and problems in school correspond to the child's level of adaptation (academic performance, mood regulation, and social relations with peers and adult authority) in the school setting. A secondary question is the extent to which patterns of adaptation in the school context relate to parental psychopathology.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02362-01 LDP

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Physical/Neurological Development in Children of Healthy and Depressed Mothers

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: T. Sherman Research Psychologist LDP/NIMH

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

Section on Affective Development

INSTITUTE AND LOCATION

National Institute of Mental Health, NIH, 9000 Rockville Pike, Bethesda, MD 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| .37 | .05 | .32 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☒ (a1) Minors
- ☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The exciting current work on the biochemical and genetic bases of the major affective disorders makes more salient the need to bridge the sciences and begin to develop concepts and markers linking the physical and neurological substrate with the complex behavioral manifestations of these disorders. A developmental framework provides a basis for moving beyond correlational assessment to causal modeling. This project will be a step in this process.

A rich body of data (Childrearing Study, Annual Report # Z01 MH 02144 ) on the children's birth complications, physical development, cognitive development and neurological development will be brought together as profiles for individual children. These profiles will be subjected to a cluster analysis. It is expected that some of the clusters of children will be associated with higher family loadings for affective illness. It is also expected that particular clusters will be associated with specific social, emotional, and/or cognitive outcomes, or with the development of symptoms of affective illness, and/or behavioral disorders in the children.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02363-01 LDP

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Information-Processing Deficits in Schizophrenic Children

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | T. Sherman | Research Psychologist | LDP/NIMH |
| Other: | R. Asarnow | Associate Professor | UCLA School of Medicine |

COOPERATING UNITS *(if any)*

UCLA School of Medicine

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

Section on Affective Development

INSTITUTE AND LOCATION

National Institute of Mental Health, NIH, 9000 Rockville Pike, Bethesda, MD 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| .37 | .05 | .32 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☒ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project was designed to add to the growing body of literature concerning core cognitive impairments in schizophrenic children. Both adult and child schizophrenics show a wide range of impairments on a variety of cognitive tasks. However, if these studies are examined carefully, it does not appear that we have been able to identify a specific process that is consistently impaired in schizophrenic individuals. This suggests that the impairment is more systemic, not simply contained within a small set of isolable information processing functions. In this study, based on the Feature Integration Theory of Attention by Treisman and Gelade, the ability of the schizophrenic child to recognize the task relevance of, and engage in, serial and parallel modes of visual search is examined. The data reveal that schizophrenic children are as competent as MA-matched control children in their use of a parallel visual search strategy and a serial visual search strategy, and in their recognition of the situations under which each is the optimal strategy. Importantly, the data also reveal that schizophrenic children have a significantly greater start-up time than the MA-matched controls in the initiation of their search strategies. This difference is in the range of 480 msecs. This is much greater than would be predicted on the basis of merely a motor delay in button pushing. These results suggest that the schizophrenic individual does not have a specific information processing deficit, but rather a global deficit in time to initiate the operation of any information processing strategy, be it an automatic strategy or an attention demanding strategy. Such a deficit would be apparent in all tasks requiring speeded information processing, and in real-time processing of information.

| DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE<br>NOTICE OF INTRAMURAL RESEARCH PROJECT | PROJECT NUMBER<br>Z01 MH 02364-01 LDP |
|---|---|

PERIOD COVERED
October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
A Follow-up Investigation of Offspring of Bipolar Parents

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | C. Zahn-Waxler | Chief, Sec. on Child Behavior Disorders | LDP/NIMH |
| Other: | L. Cytryn | Medical Officer (Psych) | LDP/NIMH |
| | A. Mayfield | Psychology Technician | LDP/NIMH |
| | D. McKnew, Jr. | Medical Officer (Psych) | LDP/NIMH |
| | M. Radke-Yarrow | Chief | LDP/NIMH |

COOPERATING UNITS *(if any)*
None

LAB/BRANCH
Laboratory of Developmental Psychology

SECTION
Section on Child Behavior Disorders

INSTITUTE AND LOCATION
National Institute of Mental Health, NIH, 9000 Rockville Pike, Bethesda, MD 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| .55 | .25 | .30 |

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☒ (a1) Minors
  ☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Seven male children of severely ill manic-depressive parents (five of whom had a unipolar depressed spouse) were studied at one and at two years of age. They showed a range of adjustment problems when assessed in a laboratory setting (protocol # 78-M-75). They had insecure attachment relationships with their caregivers and had problems in regulation of affect. Disturbances in empathy and aggression also were evident. Psychological and psychiatric assessments of the children were conducted four years later to determine whether problems identified earlier were transitory or persistent and indicated possible precursors of later diagnosable disturbance.

On the follow-up at five and six years of age, these children differed from a control group on many dimensions of functioning. In a psychiatric interview, they reported more fears, worries, symptoms of depression and distortions in self-image. Their mothers indicated a high incidence of externalizing, as well as internalizing symptoms in the children. Proband children received more formal (DSM-III) psychiatric diagnoses than control children. Deficits in empathy and non-assertive strategies for resolving conflict also were identified. Many of the problems persisted over time, even for children who were in therapy, for whom change was evident. These patterns underscore the need for early intervention in families such as these in which both parents are depressed and in which there is a familial history of affective disorder as well.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 MH 02365-01 LDP

PERIOD COVERED
October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
The Psychobiological Effects of Sexual Abuse

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | F.W. Putnam | Staff Psychiatrist | LDP NIMH |
| OTHER: | P.K. Trickett | Guest Researcher | LDP NIMH |

COOPERATING UNITS *(if any)*
Chesapeake Institute, Kensington, Maryland; Montgomery County Child Protection Unit; Prince Georges County Child Protection Unit; Virginia Child Protection Services, Fairfax County, Virginia

LAB/BRANCH
Laboratory of Developmental Psychology

SECTION
Section on Child Behavior Disorders

INSTITUTE AND LOCATION
National Institute of Mental Health, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| .37 | .25 | .12 |

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☒ (a1) Minors
☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This study focuses on the psychological and biological effects of sexual abuse on children. Subjects will be sexually abused females (6-15 years of age) and their parents or guardians. Controls will be age and socio-economically matched. The study will use a multi-method approach to gather information on the psychological and physical development of children and their home environment. Methods include: staging physical development, measurement of blood hormone levels, psychological tests and measures for both children and adults. Three hypotheses will be tested: A), that sexually abused girls will have a more difficult transition through puberty; B), that sexual abuse may alter the hormonal levels and effect the timing of puberty; and C), that sexually abused children will demonstrate higher levels of dissociation than controls.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02367-01 LDP

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

The Clinical Phenomenology of Multiple Personality Disorder

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | F.W. Putnam | Staff Psychiatrist | LDP/NIMH |
| Other: | R. Lowenstein | Chief | Dept. Psy., UCLA |
| | R. Post | Chief | BPP/NIMH |

COOPERATING UNITS *(if any)*

UCLA
Biological Psychiatry Branch

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

Section on Child Behavior Disorders

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| .47 | .35 | .12 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☒ (a1) Minors
  ☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The clinical syndrome of multiple personality disorder (MPD) is an unusual dissociative disorder that previously had been poorly characterized. Systematic data have been collected on over 200 recent cases of MPD in treatment in the United States. Results indicate that MPD is a clinical syndrome with a core of dissociative and depressive symptoms that occurs in individuals with a history of childhood trauma between ages 2 and 14 years. Male and female MPD patients differ on the expression of aggressive and self-destructive symptoms.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02368-01 LDP

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

The Dissociative Experiences Scale (DES)

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: F.W. Putnam Staff Psychiatrist LDP NIMH

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

Section on Childhood Behavior Disorders

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| .37 | .25 | .12 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☒ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

A short, self-administered questionnaire, the Dissociative Experience Scale (DES), has been developed and tested. The DES reliably and validly measures frequency and types of dissociative phenomena. This instrument has been administered to a wide variety of carefully diagnosed psychiatric groups. The DES has been included in over 50 studies in the United States and abroad and has been translated into French, Dutch and Cambodian. Current research using this instrument includes studies of patients with epilepsy, eating disorders, borderline personality disorder, affective disorders and schizophrenia in conjunction with researchers in the IRP, NIMH; NINCDS; and the Department of Psychiatry, UCLA and the Department of Psychology, The American University.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02369-01 LDP

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Mutual Interpersonal Influence in Families with and Without Affective Disorder

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: G. Kochanska Research Psychologist LDP/NIMH

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, Maryland 20892

| | | |
|---|---|---|
| TOTAL MAN-YEARS:<br>.77 | PROFESSIONAL:<br>.35 | OTHER:<br>.42 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☒ (a1) Minors
  ☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Processes of mutual interpersonal influence are studied in dyads comprised of well and depressed mothers and their 5-year-old children. This is a longitudinal study, following up the sample of 87 dyads, in which control and discipline interactions were studied when the children were 1 1/2 to 3 1/2 years old (Z01 MH 02152). Two major themes are followed: difficulties of depressed mothers in controlling their children, which were identified in the original study, and the development of children's competent interpersonal strategies of influence, which in their emerging form were studied in toddler period. In contrast to the first study, where the focus was on the mother as the agent of control and child as a respondent, in this study the focus is on bilateral interpersonal influence processes. Every episode of control, which can be initiated either by the mother or by the child, is coded.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02370-01 LDP

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Caregiving Patterns in Stressed Families

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | F. Bridges-Cline | Guest Researcher | LDP/NIMH |
| Other: | W.E. Wilson | Research Psychologist | DRG/NIH |
| | M. Radke-Yarrow | Chief | LDP/NIMH |
| | D. Hay | Research Psychologist | Univ. of London |
| | T. Cox | Psychiatrist | Univ. of Liverpool |

COOPERATING UNITS *(if any)*

University of London
Division of Research Grants, NIH
Univ. of Liverpool

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| .37 | .05 | .32 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☒ (a1) Minors
☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Experiences in the family are presumed to play a significant role in the socialization of the child, the development of his or her personality, and the emergence of any pathological characteristics. Of primary interest in this research is the functioning of different sorts of families with respect to a central dimension of family life, the provision of care to its members. An immediate objective of this study is the development of a behavioral family interaction coding system that focuses on the giving and receiving of care among family members. The goal is for the coding system to be at the same time sufficiently broad in the conceptualization of "caregiving" as to be applicable to family life in different cultures and family members of different ages, and sufficiently articulated as to be capable of differentiating families with and without varying kinds of internal and external stressors. An additional aim of the study is the examination of associations of parental depression and other family stressors with varying patterns of family caregiving. This aim derives from the view that family caregiving is a potential mediator of factors such as economic distress or parental pathology that place children at risk for later problems. In this regard, the coding system is being piloted, refined, and used on a sample of disadvantaged families in Britain and a sample of families in the NIMH study, with and without parental depression.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

**NOTICE OF INTRAMURAL RESEARCH PROJECT**

PROJECT NUMBER

Z01 MH 02371-01 LDP

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Patterns of Alliance in Families with and Without Parental Depression

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | F. Bridges-Cline | Guest Researcher | LDP/NIMH |
| Other: | W. Wilson | Research Psychologist | DRG/NIH |

COOPERATING UNITS *(if any)*

Division of Research Grants, NIH

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| .22 | .10 | .12 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☒ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

One of the ways in which parental depression may influence the development of the child is through the kinds of affective involvement that characterize the relationships among various members of the family. These patterns of affective involvement within and across family subsystems (i.e. the spouse, parent-child, and sibling subsystems) are significant contributors to the child's development not only through their influence on the pervasive emotional climate of the environment within which the child functions but also through their influence on the child's developing understanding of self in relationships. Within the family systems literature, this aspect of family member relationships (i.e. the direction and degree of affective responsiveness) has been referred to as "alliances"; and it has been found that the pattern and nature of alliances are quite different in distressed and dysfunctional as compared to effectively functioning families. The aim of this study is to examine the nature and pattern of family alliances--the availability and strength of interfamily communication channels and the affective quality of these communications--in families with and without parental depression.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02372-01 LDP

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Psychiatric Status of Children of Depressed Parents

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | M. Radke-Yarrow | Chief | LDP/NIMH |
| Other: | L. Cytryn | Med. Officer (Psychiatry) | LDP/NIMH |
| | D. McKnew | Med. Officer (Psychiatry) | LDP/NIMH |
| | L. Kuczynski | Assoc. Professor | Univ. of Guelph |
| | T. Sherman | Research Psychologist | LDP/NIMH |
| | E. Nottelmann | Statistician | LDP/NIMH |

COOPERATING UNITS *(if any)*

University of Guelph, Guelph, Ontario

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1.77 | .95 | .82 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☒ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

There is very little research that provides prospective data on the developmental course of offspring of depressed parents. At each of the developmental periods at which we have seen the children (younger child at 2 to 3 years, followed up at 5 to 6 years; older sibling 5 to 8 years, followed up at 8 to 11 years), psychiatric assessments have been made, to be related to parental diagnostic status, family environmental variables, and developmental variables. In analyses to date, we have focused on associations between parental diagnoses and children's psychiatric status. At 2 to 3 years of age, assessments did not differentiate the children by diagnosis of parents. About 10% of the children were rated at risk in the well and in the depressed parent groups.

We analyzed the children of middle-class background, who were initially seen as toddlers, at their first follow-up assessment. At this time they manifested problems (DSM-III diagnoses) with different frequencies depending on parental diagnosis, i.e., 15% of the children of well parents, 21% of the children of depressed mothers and well fathers, and 47% of the children of depressed mothers and fathers. When their siblings were seen at 8 to 11 years, the corresponding percentages were 8%, 28%, and 53%. The same data were re-examined in relation to unipolar and bipolar maternal depression. There was little difference in the frequencies of problems in these two groups.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

## NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02379-01 LDP

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Survivor Children

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | M. Radke-Yarrow | Chief | LDP NIMH |
| OTHER: | T. Sherman | Research Psychologist | LDP NIMH |

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1.12 | .35 | .77 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☒ (a1) Minors
- ☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The focus of this study is on children who by criteria of genetic and family variables are at high risk, but who are functioning relatively well. Criteria of high risk were both parents are depressed or mother is depressed and father is absent, and family environment is stressful. Fifty children, two from each of 25 families that met these criteria of risk, were studied. The children were between 5 and 11 years. In-depth case analyses were done on four children who were functioning well; namely, had no diagnosis; were liked by parents, teachers and peers; and were performing at grade level. On this basis, critical factors in their development were identified and hypotheses regarding conditions or processes promoting good functioning were formulated and tested on the 50 children to determine whether the identified factors predicted the current status of the children in the high risk sample.

The protective factors shared by all of the children who were "surviving" were above average intelligence, had socially winning ways or charm, and a match, since birth, between a specific characteristic of the child and a parental need. By fulfilling a specific need of the ill parent(s), the "survivor" children have received the maximum support from their family's scant psychological resources. The children's relatively good functioning is, however, at the expense of their own developmental needs.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

**NOTICE OF INTRAMURAL RESEARCH PROJECT**

PROJECT NUMBER

Z01 MH 02380-01 LDP

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Stressful Life Events and Childhood Adjustment

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | J. E. Richters | Research Psychologist | LDP/NIMH |
| Other: | D. Pellegrini | Psychologist | Catholic Univ. |
| | M. Radke-Yarrow | Chief | LDP/NIMH |

COOPERATING UNITS *(if any)*

Catholic University

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| .77 | .30 | .47 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

- ☒ (a1) Minors
- ☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project is designed to investigate the links between parental psychopathology, stressful life events, and the social-emotional adjustment of children at-risk. The analyses are based on data from families participating in the NIMH Childrearing Project (Z01 MH 02144), which includes children of parents with and without a history of affective disorder. Assessments of parental psychopathology are based on psychiatric (SADS-L) interviews with each parent. Stressful life events to which the children have been exposed are assessed on the basis of intensive, semi-structured interviews with mothers. Evaluations of children's functioning are based on psychiatric interviews, direct observations of their behavior in our laboratory apartment, and independent reports from their parents and teachers.

In an initial set of analyses, characteristics of stressful events (e.g. nature, severity, timing, frequency, saturation) are coded without coders' knowledge of children's responses to the events. Events and characteristics of events that are caused, exacerbated, or buffered by parental functioning are distinguished. Associations between these subsets of stressful events and their characteristics to predictions of offspring adjustment will be examined.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

**NOTICE OF INTRAMURAL RESEARCH PROJECT**

PROJECT NUMBER

Z01 MH 02381-01 LDP

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Functioning of Depressed Mothers Within and Between Episodes

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | J.E. Richters | Research Psychologist | LDP/NIMH |
| Other: | M. Radke-Yarrow | Chief | LDP/NIMH |

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| .77 | .30 | .47 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☒ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

What are the characteristic differences between depressed and non-depressed women in their interactions with and around their children? Are maternal child-related behavioral deficits characteristic of women with a history of depression, or are difficulties present only when mothers are experiencing an acute episode of depression? More broadly, are there certain patterns of aberrant child-related behaviors that wax and wane with depressive episodes, and others that reflect more or less enduring behavioral characteristics of depressed mothers? These questions are important to the study of depressed women as mothers and their influence on children.

The NIMH Childrearing Project is in a unique position to explore this issue, by comparing maternal characteristics of two groups of mothers with a history of affective disorder: those who are within and those who are between episodes of depression at the time of their participation in our laboratory apartment at follow-up. These groups of mothers will be compared on symptom-related behaviors and interactive behaviors, including patterns of 1) eliciting compliance and cooperation from their children, 2) monitoring of and responsiveness to their children's need states, 3) displays of affect such as anger and affection, 4) patterns of content and topography in verbal interactions, and 5) methods of resolving conflict between offspring siblings. Parallel analyses will be conducted using self-reported mood as a basis for regrouping mothers; this will allow us to address more general state-trait questions beyond those that are specific to depressive episodes, per se.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

**NOTICE OF INTRAMURAL RESEARCH PROJECT**

PROJECT NUMBER

Z01 MH 00478-31 LN

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Neural mechanisms of cognitive memory and habit formation

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | M. Mishkin | Chief | LN NIMH |
| Others: | E.A. Murray | Senior Staff Fellow | LN NIMH |
| | J. Bachevalier | Visiting Scientist | LN NIMH |
| | R.C. Saunders | Staff Fellow | LN NIMH |
| | D.P. Friedman | Project Officer | NRB NIDA |

COOPERATING UNITS *(if any)*

National Institute on Drug Abuse

LAB/BRANCH

Laboratory of Neuropsychology

SECTION

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 9.0 | 2.5 | 6.5 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Every sensory modality in the macaque is served by a series of cortical stations, each of which processes the sensory signal in turn. Signals in the later stations, located in the anterior temporo-insular cortex, can activate a circuit that runs through the limbic system to the modulatory neurochemical systems (e.g. cholinergic, noradrenergic, etc.) and back to the sensory cortical stations. We have proposed that as a result of the action of this circuit on neurochemical release in sensory cortex, some of the neurons whose signals have just represented the sensory stimulus become linked together in a cell assembly that serves as the stored representation of that stimulus. Recognition, say of an object, occurs when an assembly formed on a first presentation of the object is reactivated by its re-presentation on a second occasion. Also, once formed, that assembly can be linked to assemblies representing other stimuli and other events, such as a food reward or a location, thereby investing the recognized object with meaning. The linkage involved in object-reward association appears to be mediated mainly by a limbo-neurochemical circuit running through the amygdala, the medial dorsal thalamic nucleus, orbital frontal cortex, and the basal nucleus of Meynert. Similarly, the linkage involved in object-place association seems to be mediated mainly by a second, parallel limbo-neurochemical circuit running through the hippocampus, the anterior thalamic nuclei, cingulate cortex, and the medial septal and diagonal band nuclei. Each of these circuits has reciprocal connections with one pair or the other of the assemblies described above. Thus, if these circuits have been activated, the sight of the object on a second occasion can lead not only to its recognition but also to recall of both the food reward and the spatial location with which the object had been associated. Recognition and recall are two forms of cognitive memory, both of which can be distinguished from habit formation. The latter form of learning involves stimulus-response association specifically, and we have proposed that such learning depends largely on interactions between the cerebral cortex and the basal ganglia.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02032-11 LN

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Neural coding of visual stimuli in the awake monkey

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

| | | | |
|---|---|---|---|
| PI: | B.J. Richmond | Senior Surgeon | LN NIMH |
| Others: | L. Optican | Senior Staff Fellow | LSR NEI |
| | M. Mishkin | Chief | LN NIMH |

COOPERATING UNITS (if any)

Laboratory of Sensorimotor Research, NEI

LAB/BRANCH

Laboratory of Neuropsychology

SECTION

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 2.0 | 1.0 | 1.0 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Single neurons were recorded from the lateral geniculate nucleus and primary visual cortex, the first two extraretinal stages of visual processing, and inferior temporal cortex, the last visual cortical processing station, to study the mechanisms underlying visual perception. Neurons in all three regions showed different temporal response patterns to different visual stimulus patterns. When these neurons were analyzed as communication channels carrying information about visual stimuli in their responses, the response patterns seen could only be represented as the sum of several (3-6) simultaneous, independent patterns of activity. Three of these activity patterns were analyzed as a temporal code, and the information contained in them was compared to the information conveyed by the number of action potentials, the usual measure of neuronal response; there was twice as much information available in the temporal code. This showed that each response can be considered the sum of activity from several independent channels, with each channel acting as a spatial-to-temporal filter. Traditionally, it has been thought that information about multiple stimulus parameters, such as luminance, pattern, and duration of presentation, must be confounded in the neuronal responses. However, based on this multiplex-filter hypothesis, a new analysis of the primary visual cortex responses led to the discovery that information about each of these parameters is carried separately in the response. This strongly suggests that a consistent neural code exists. A geometrical analysis of these data shows a potential structure for this code. When a 3-dimensional space is used to represent the responses, the responses to a single pattern appear to lie in a plane regardless of luminance or duration. For a single neuron's response, the planes for different patterns are frequently separable. The equations for these planes describe a neural code.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02033-10 LN

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Functional mapping of sensory and memory systems

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | R.C. Saunders | Staff Fellow | LN NIMH |
| Others: | M. Mishkin | Chief | LN NIMH |
| | J. Bachevalier | Visiting Scientist | LN NIMH |
| | C. Kennedy | Guest Researcher | LCM NIMH |
| | L. Sokoloff | Chief | LCM NIMH |

COOPERATING UNITS *(if any)*

Laboratory of Cerebral Metabolism, NIMH

LAB/BRANCH

Laboratory of Neuropsychology

SECTION

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 0.5 | 0.5 | 0 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The cerebral areas related to vision in the rhesus monkey were identified by comparison of metabolic activity in visually stimulated versus visually deafferented cerebral hemispheres. The results allowed delineation of the visual-nonvisual borders of both an occipitotemporal and an occipitoparietal visual pathway and specification of their points of interaction with frontal, limbic, striatal, and diencephalic structures. In addition, it was found that, within the occipitotemporal pathway, the forebrain commissures contribute to the visual activation of area TE only.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02035-07 LN

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Anatomy of the primate visual system

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

| | | | |
|---|---|---|---|
| PI: | L.G. Ungerleider | Research Psychologist | LN NIMH |
| Others: | M. Mishkin | Chief | LN NIMH |
| | R. Desimone | Research Psychologist | LN NIMH |
| | D. Boussaoud | Visiting Fellow | LN NIMH |
| | R.J. Tusa | Assistant Professor | Johns Hopkins Univ. |

COOPERATING UNITS (if any)

Johns Hopkins University

LAB/BRANCH

Laboratory of Neuropsychology

SECTION

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland

| TOTAL MAN-YEARS. | PROFESSIONAL | OTHER |
|---|---|---|
| 4.75 | 2.0 | 2.75 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

To better understand the role of visual association cortex in perception and memory, we have been examining the functional areas that comprise this cortex in the macaque and exploring their interconnections by the use of neuroanatomical tracing techniques in combination with electrophysiological recording of neural activity. Our results indicate that a multiplicity of separate visual areas lie beyond the primary visual cortex, or striate cortex (V1), in the stream of information processing. These areas are organized into two divergent corticocortical pathways, each having V1 as the source of its initial input. One, an occipitotemporal pathway, enables the visual recognition of objects, while the other, an occipitoparietal pathway, mediates the appreciation of the spatial relationships among objects as well as the visual guidance of movements toward objects in space. The visual areas along the occipitotemporal pathway (V1, V2, V3, V4, and areas TEO and TE of the inferior temporal cortex) appear to be organized primarily as a serial hierarchy, in which each area processes both color and form information. By contrast, the areas along the occipitoparietal pathway (V1, MT, and MT's projection zones in parietal cortex) process the direction of stimulus motion. Because a major component of this pathway extends anteriorly within the superior temporal sulcus, the neural mechanisms underlying visuospatial function may be more extensive than previously thought. To establish the links of both the occipitotemporal and occipitoparietal pathways with the motor system, we have been exploring the projections of visual association cortex to the striatum. So far, we have found that TE, TEO and V4 all project to the tail of the caudate nucleus and ventral putamen, an arrangement that contrasts with the pattern of projections from the occipitotemporal pathway to the limbic system, which arise from TE only. The presence of direct projections to the striatum but not to the limbic system from V4 and TEO may explain the ability of monkeys with TE lesions to acquire visual habits but not visual memories.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02036-07 LN

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Neural representations of visual stimuli in the extrastriate cortex

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

| | | | |
|---|---|---|---|
| PI: | R. Desimone | Research Psychologist | LN NIMH |
| Others: | M. Mishkin | Chief | LN NIMH |
| | H. Spitzer | Visiting Associate | LN NIMH |

COOPERATING UNITS (if any)

LAB/BRANCH

Laboratory of Neuropsychology

SECTION

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS | PROFESSIONAL: | OTHER: |
|---|---|---|
| 2.5 | 1.25 | 1.25 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Disorders of perception, attention, and memory frequently accompany the major mental diseases. To begin to understand the neural mechanisms of these mental processes, we are recording the activity of neurons in the extrastriate cortex of monkeys engaged in tasks requiring visual discrimination, selective attention, and recognition memory. We have found in area V4 of the occipital cortex and area TE of the inferior temporal cortex that selective attention gates visual processing by filtering unwanted information from the receptive fields. Even the degree to which attended stimuli are processed in these areas depends on "how much" attention or effort is devoted to them. Thus, the information-processing capacity of cortical neurons depends not only on hard-wired mechanisms but on cognitive state. To identify the mechanisms by which cognitive state modulates cortical activity, we have begun to examine both extrastriate neuronal activity and animal behavior in an attention-demanding task following lesions of selective portions of the prefrontal cortex, posterior parietal cortex, limbic-system, and basal ganglia.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02037-06 LN

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Functional anatomy of the somatosensory cortex of the monkey

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | T.P. Pons | Guest Researcher | LN NIMH |
| Others: | M. Mishkin | Chief | LN NIMH |
| | D.P. Friedman | Project Officer | NRB NIDA |
| | E.A. Murray | Senior Staff Fellow | LN NIMH |
| | R.J. Schneider | Guest Researcher | LN NIMH |
| | R.C. Saunders | Staff Fellow | LN NIMH |
| | P.E. Garraghty | Research Associate | Vanderbilt Univ. |

COOPERATING UNITS *(if any)*

National Institute on Drug Abuse
Vanderbilt University

LAB/BRANCH

Laboratory of Neuropsychology

SECTION

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 0.25 | 0 | 0.25 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

To identify a route by which tactile information could reach limbic structures in the temporal lobe, we used axonal transport techniques to trace the connections between somatosensory cortical fields. On the basis of the laminar patterns of these corticocortical connections, we identified them as 'forward' or 'backward' by analogy to similar designations in the visual system, where they have been shown to have functional validity. The analysis indicated that a forward-projecting route could be traced from the subdivisions of the primary somatosensory cortex to the second somatosensory area, SII; from SII to the granular and dysgranular fields of the insula; and from the insula directly to the amygdala and indirectly to the hippocampus via rhinal cortex. This multisynaptic cortico-limbic pathway in the somatosensory system is thus organized in a manner analogous to the multisynaptic cortico-limbic pathway in the visual system. To assess the functional importance of the pathway, we studied the somatosensory receptive fields of neurons in SII cortex following selective ablations within the primary somatosensory cortex and found that elimination of any given representation of the body surface in the postcentral strip eliminated it also in SII. For example, removing the hand representation from the postcentral strip resulted in its disappearance from SII cortex; conversely, removing all other body representations from the post central strip (i.e. except that of the hand) resulted in the preservation in SII of the hand representation only. The electrophysiological data thus provide strong support for the conclusion, based originally on the anatomical data, that tactile information is processed sequentially along a corticortical pathway. The electrophysiological experiments also revealed a surprising degree of functional reorganization in SII cortex following the postcentral cortical ablations. After each partial removal, the vacated representation in SII was filled in by the expansion of the intact, neighboring representations. These last findings point to a previously unrecognized degree of cortical plasticity in adult primates following

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02038-05 LN

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Ontogenetic development of cognitive memory and habit formation

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | J. Bachevalier | Visiting Scientist | LN NIMH |
| Others: | M. Mishkin | Chief | LN NIMH |
| | L.G. Ungerleider | Research Psychologist | LN NIMH |
| | D.P. Friedman | Project Officer | NRB NIDA |
| | C. Hagger | Guest Researcher | LN NIMH |
| | P. Merjanian | Guest Researcher | LN NIMH |

COOPERATING UNITS *(if any)*

National Institute on Drug Abuse

LAB/BRANCH

Laboratory of Neuropsychology

SECTION

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 2.25 | 1.0 | 1.25 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Cognitive memory and habit formation are two qualitatively different learning processes based on separate neural systems, a cortico-limbic and a cortico-nonlimbic system, respectively. To see how emotional and social behavior develop in animals whose infantile global amnesia might persist from infancy through adulthood, we have prepared monkeys with neonatal limbic lesions and followed their behavioral development. Animals with neonatal removal of cortical area TE, a higher-order visual station linked to both learning systems, serve as controls. The results indicate that neonatal TE lesions leads to a transient impairment of habit formation three months later (compared to permanent impairment seen with the same lesion in adults), whereas both neonatal and adult limbic lesions leave habit formation intact. Interestingly, data on both normal and operated infants suggest that development of the nonlimbic habit system is sexually dimorphic, and that this is due to the high testosterone levels present in male infants before and shortly after birth. At ten months of age, the infants with limbic lesions show impairment in memory formation, whereas the operated controls show significant functional sparing (compared to those that received the same lesions as adults). These findings point to greater compensatory potential after neonatal cortical than after neonatal limbic removals, indicating that association areas of the cortex are immature at birth, and may thus possess greater plasticity than limbic structures. Direct evidence of neocortical immaturity in the macaque has been provided by our neurobiological studies on opiatergic and cholinergic receptor distribution and on metabolic activity. Finally, early damage to the limbic memory system produces later socio-emotional abnormalities that are similar in many respects to the behavioral syndrome seen in autistic children.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02039-05 LN

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Pharmacology of cognitive memory and habit formation

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | T.G. Aigner | Senior Staff Fellow | LN NIMH |
| Others: | M. Mishkin | Chief | LN NIMH |
| | R.Q. Wan | Visiting Fellow | LN NIMH |
| | R.M. Brown | Chief | NS NIDA |
| | M.R. DeLong | Professor | Johns Hopkins Univ. |
| | D. Price | Professor | Johns Hopkins Univ. |

COOPERATING UNITS *(if any)*

The Johns Hopkins University School of Medicine
National Institute on Drug Abuse

LAB/BRANCH

Laboratory of Neuropsychology

SECTION

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 3.0 | 2.0 | 1.0 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Evidence from patients with Alzheimer's disease suggest that the basal forebrain cholinergic system plays an important role in memory. In support of this proposal, we have found impaired visual recognition memory in monkeys with lesions to the major nuclei of this system. We have found further that recognition memory in normal monkeys can be improved by the cholinesterase inhibitor physostigmine and impaired by the cholinergic muscarinic-receptor blocker scopolamine. In addition, our results indicate that scopolamine acts at a very early stage of memory, preventing information from entering even into an immediate store.

Based on previous results indicating that THC may be exerting its effects through an action on the limbic system, we administered this drug to monkeys performing spatial reversal, a task known to be sensitive to hippocampal damage. Doses equal to or even greater than those that impaired recognition memory did not affect performance on this task, though performance did appear to be affected several days after the last dose of THC, raising the possibility of a delayed abstinence effect.

In a series of experiments on habit formation, we administered the dopaminergic-neurotoxin MPTP to monkeys, but failed to show learning impairments at doses that did not also impair motor function. Administration of MPTP did make the animals more sensitive to the disruptive effects of scopolamine, however, suggesting that the cholinergic-dopaminergic balance in the neostriatum had been compromised.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02040-04 LN

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Functional analysis of neurotransmitter systems

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

| | | | |
|---|---|---|---|
| PI: | T.P. Pons | Guest Researcher | LN NIMH |
| Others: | M. Mishkin | Chief | LN NIMH |
| | D.P. Friedman | Project Officer | NRB NIDA |
| | J. Bachevalier | Visiting Scientist | LN NIMH |
| | L.G. Ungerleider | Research Psychologist | LN NIMH |
| | C.B. Pert | Chief, Sec. Brain Chemistry | NSB NIMH |
| | A. Routtenberg | Professor | Northwestern Univ. |

COOPERATING UNITS (if any)

National Institute on Drug Abuse
Section on Brain Chemistry, NIMH
Northwestern University

LAB/BRANCH

Laboratory of Neuropsychology

SECTION

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

| | | |
|---|---|---|
| TOTAL MAN-YEARS: 0 | PROFESSIONAL: 0 | OTHER: 0 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This project has been terminated.

|  |  |
|---|---|
| DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE<br>NOTICE OF INTRAMURAL RESEARCH PROJECT | PROJECT NUMBER<br>Z01 MH 00471-32 LPP |

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Studies of Heredity and Environment in Schizophrenia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: Allan F. Mirsky, Ph.D. Chief LPP, NIMH

COOPERATING UNITS *(if any)*

Institute for Research on Kibbutz Education, Haifa University, Israel; Hebrew University, Israel; Oranim Teacher's College, Israel; Bar Ilan University, Israel; University of Chicago, Illinois

LAB/BRANCH

Laboratory of Psychology and Psychopathology

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, Bethesda, Maryland 20892

|  |  |  |
|---|---|---|
| TOTAL MAN-YEARS:<br>1.5 | PROFESSIONAL:<br>1.0 | OTHER:<br>0.5 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☒ (a1) Minors
- ☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project has been composed of the following studies: (1) An intensive multi-disciplinary study of a family with MZ quadruplets (daughters) concordant as to schizophrenia but discordant as to severity and outcome; (2) Studies of Danish adoptees and their biological and adoptive families; (3) A study of children (of schizophrenic and control parents) reared in town or kibbutz in Israel. We maintain contact with the quadruplets but have not pursued active studies with them during the past two years. The Danish adoptees are of continuing interest to us and we are preparing additional reports on factors involved in their psychiatric outcome. The Israeli children are the subject of intensive research efforts and we are currently conducting further behavioral and biological studies with them.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00484-27 LPP

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Psychophysiological Responsivity and Behavior in Schizophrenia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: Theodore P. Zahn, Ph.D. Research Psychologist LPP, NIMH

COOPERATING UNITS *(if any)*

Laboratory of Socio-Environmental Studies, Child Psychiatry Branch, Laboratory of Clinical Science, Neuroscience Branch, Biological Psychiatry Branch, and Clinical Neurogenetics Branch, NIMH; Hypertension-Endocrine Branch, NHLBI.

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Laboratory of Psychology and Psychopathology

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NIMH, ADAMHA, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1.7 | 0.8 | 0.9 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☒ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The general purpose of this project is to investigate the roles of autonomic nervous system (ANS) activity, attention, and information processing and their interrelationships in the pathology, etiology, and prognosis of psychiatric disorders. A second purpose is to determine biological and psychological processes related to ANS activity and attention. ANS activity is assessed by peripheral measures, such as skin conductance, heart rate, and skin temperature. Subjects are tested under conditions of rest, presentation of tones, and performance on tasks such as reaction time and mental arithmetic.

Biological mechanisms are investigated by correlating these variables with enzyme activity, neuropeptides, and levels of biogenic amines and their metabolites and with brain dysfunction as revealed by CT and PET scans.

Studies are being done on unmedicated patients with diagnoses of schizophrenia, affective disorder, obsessive compulsive disorder, anxiety-panic disorder, and autism to test the diagnostic specificity of patterns of ANS activity. Children of parents with bipolar affective disorder are being studied to determine a possible ANS trait markers. In some studies blood samples are taken during ANS recording sessions in which stressful procedures are given. In one, the effects of success and failure to escape an aversive noise are assessed, and in another, the effects of a dose of yohimbine is being studied. Clinical trials of various treatments are studied in various groups.

Psychological correlates are studied via clinical background data, clinical ratings and questionnaires, and by procedural variations. The use of confirmatory factor analysis in data reduction and to improve quantification of ANS activity is being explored.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00486-15 LPP

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Psychophysiological Effects of Stimulant Drugs in Children

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | Theodore P. Zahn, Ph.D. | Research Psychologist | LPP, DIRP, NIMH |
| Other: | Judith Rapoport, M.D. | Chief | CHP, NIMH |
| | Martine Flament, M.D. | Guest Researcher | CHP, NIMH |
| | Marcus Kruesi, M.D. | Clinical Associate | CHP, NIMH |

COOPERATING UNITS *(if any)*

Child Psychiatry Branch, NIMH

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SECTION

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NIMH/ADAMHA, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 0.3 | 0.2 | 0.1 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☒ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Tests of the effects of acute and chronic administration of caffeine on autonomic nervous system (ANS) functioning have been carried out to evaluate the role of ANS activity in the behavioral and subjective effects of this drug. A test of attention using a reaction time method is included.

The test protocol involves recording peripheral indicators of ANS activity such as skin conductance (SC), heart rate (HR), and skin temperature during a session consisting of a rest period, presentation of a series of simple tones to which no response is required, and the reaction time task. Studies have been carried out on the effects of the acute administration of two doses of caffeine and a placebo in 6-13 year old boys and in men, and a study of chronic (2 week) caffeine intake in children.

The effects of both acute and chronic administration of caffeine were increases in SC indices of arousal but some trends toward decreases in HR. The SC results are consistent with the hypothesis that caffeine can be considered a pharmacologic model for anxiety, but the HR effects suggest the model is imperfect.

The most recent study, an acute dose protocol with caffeine was conducted on children with anxiety disorders and controls. This tested the hypothesis, for which there is evidence in adults, that patients with anxiety disorders are more sensitive to caffeine than controls.

Another current study compares ANS activity and attention in boys with diagnoses of Conduct Disorder and Attention Deficit Disorder.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00491-11 LPP

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Personality Factors and Psychophysiological Responses to Changing Stimulus Input

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | Theodore P. Zahn, Ph.D. | Research Psychologist | LPP, NIMH |
| Other: | Thomas N. Robinson, Jr. | Guest Researcher | LPP, NIMH |

COOPERATING UNITS *(if any)*

NIH Normal Volunteer Office.

LAB/BRANCH

Laboratory of Psychology and Psychopathology

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, Bethesda, Maryland 20892

| | | |
|---|---|---|
| TOTAL MAN-YEARS: 0.50 | PROFESSIONAL: 0.5 | OTHER: 0.0 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The objectives of this project are to investigate relationships among differences in personality, sensory thresholds, and autonomic nervous system (ANS) activity in normal humans and to study racial differences in ANS activity. Bilateral skin conductance and heart rate have been recorded in two sessions in which constant and variable intensity tones and lights are presented and auditory and two-flash thresholds (TFT) determined by methods which permit signal detection analyses. A procedure for determining the uncomfortable loudness level has also been used. Several standardized personality tests were also given. These include scales of sensation-seeking, extraversion, neuroticism, psychoticism, field dependence and anxiety. In addition comprehensive measures of lateral dominance have been given as well as a measure of "torque" (clockwise drawing of circles) which has been hypothesized to reflect a neurointegrative deficit and be related to risk for future psychopathology. A procedure for manipulating ANS arousal experimentally with minimal distracting effects--a change in posture from supine to standing--is being used to study such problems as the effects of base levels on responsivity, the effects of arousal on performance, and the effects of personality variables on this relationship. This project allows testing of several theoretical models of the relationships of ANS activity, sensory sensitivity, and personality, some of which have implications for the etiology of psychopathology. Tests of the relationships between laterality in skin conductance variables and behavioral laterality will also be done to see if inferences about lateralized brain function can be made from such variables.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00503-07 LPP

PERIOD COVERED
October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Human Clinical Studies of Attention Disorders

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: Allan F. Mirsky Chief LPP, NIMH

COOPERATING UNITS *(if any)*

Epilepsy Branch, NINCDS; Clinical Neurosciences Branch, NINCDS; Laboratory of Clinical Sciences, NIMH; Neuropsychiatry Branch, NIMH; Boston University

LAB/BRANCH
Laboratory of Psychology and Psychopathology

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INSTITUTE AND LOCATION
NIMH, ADAMHA Bethesda, Maryland 20892

| | | |
|---|---|---|
| TOTAL MAN-YEARS:<br>2.0 | PROFESSIONAL:<br>1.25 | OTHER: |

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☒ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This research comprises three related areas of investigation concerned with specifying neuropsychological factors underlying clinical conditions in humans in which disturbed attention is a major symptom. A major emphasis is on (1) illuminating the nature of brainstem pathophysiology, if any, in such entities as petit mal or absence epilepsy, infantile autism, schizophrenia, and related diseases; (2) an additional major emphasis is on extending the neurobehavioral analysis of attention loss in absence epilepsy so as to facilitate developing alternative treatment strategies for such patients. Both of these projects form part of a larger effort which is aimed at (3) developing a comprehensive and systematic taxonomy of attentional disorders in humans. This latter study will eventually comprise study of patients with cerebral lesions, seizures, dementing diseases, and metabolic illnesses of the brain.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00504-07 LPP

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Models in the Monkey of Generalized Seizures of the Absence Type

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | Allan F. Mirsky, Ph.D. | Chief | LPP, NIMH |
| Others: | Eva Bakay Pragay, Ph.D. | Guest Researcher | Vienna<br>Austria |
| | Richard Nakamura, Ph.D. | Guest Researcher | |
| | Michael Myslobodsky, M.D., Ph.D. | Professor,<br>Univ. of Tel Aviv | Israel |
| | Richard Coppola, Ph.D. | Engineer | CBD Branch<br>NIMH |

COOPERATING UNITS *(if any)*

Tel-Aviv University, Israel

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NIMH, ADAMHA, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 0.7 | 0.7 | 0.0 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Generalized seizure activity with the electrographic appearance of absence epilepsy (bilaterally symmetrical and synchronous paroxysmal three-per-second spike and wave discharges) can be elicited in the monkey by a variety of methods. These include electrical stimulation of various locations within the brain, injection of convulsant drugs and other substances, and administration of compounds which may alter normal inhibitory mechanisms within the cell. Model seizure states created in these ways are studied in order to test hypotheses about pathophysiological seizure mechanisms, sensory processing and attentional capacities during absence seizures, effects of spike-wave activity on cellular activity, and effects of techniques or maneuvers which may modify or reduce convulsive activity. Most recently this project has involved the following work: we studied the behavioral and electrographic effects of a GABA-enhancer and surveyed the attention-related cells in the frontal lobes of the monkey. Other studies of "attention" cells in inferior parietal and preoccipital cortex have been completed as well.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00508-05 LPP

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Neuropsychological Evaluation of Psychiatric and Neurological Patients

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: Connie C. Duncan, Ph.D. Chief, Unit on Psychophysiology LPP, NIMH

COOPERATING UNITS *(if any)* Biological Psychiatry Branch, Laboratory of Clinical Science, NIMH; Developmental and Metabolic Neurology Branch, NINCDS; Chestnut Lodge Hospital; Johns Hopkins University; Maryland Head Injury Foundation; Division of Neuropsychology, Department of Psychiatry, Medical College of Pennsylvania.

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NIMH, ADAMHA, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1.7 | 0.7 | 1.0 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☒ (a1) Minors
- ☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

A set of comprehensive neuropsychological test batteries is used to provide a complete assessment of various cognitive and sensory functions that can be related to damage or dysfunction in different regions of the brain. The adult battery comprises tests designed to tap the following aspects of behavior: attention, executive functions, language, memory, motor functions, orientation, selected sensory and perceptual functions, vigilance, and visual-spatial functions. In addition, adults are given a test of general intelligence and a personality inventory. In some studies, subjects are administered a structured psychiatric interview. Modified batteries have been developed for the assessment of infants, preschool children, children ages 5-8, and children ages 6-16. The data provided by these batteries are being used to construct neuropsychological profiles of the neurological and psychiatric diagnostic groups under study in the LPP. The LPP has been particularly interested in disorders involving impaired attention, including schizophrenia, complex partial seizures, eating disorders, affective disorders, and head injuries. Comparisons are being carried out between the neuropsychological profiles of various groups of psychiatric patients and those of patients with known cerebral lesions in specified brain regions. Our data are also being used to delineate neurobehaviorally-defined subgroups within diagnostic categories, an undertaking aimed at reducing variability in psychiatric diagnosis, treatment, and outcome. The data provided by this protocol provide a complete behavioral assessment that may be integrated with concurrently gathered neurophysiological, neuroradiological, and biochemical information.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00509-05 LPP

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Attention Disorders As Assessed by Event-Related Brain Potentials

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: Connie C. Duncan, Ph.D., Chief, Unit on Psychophysiology, LPP, NIMH

COOPERATING UNITS *(if any)* Clinical Psychobiology Branch, Neuropsychiatry Branch, Laboratory of Clinical Science, Child Psychiatry Branch, NIMH; Chestnut Lodge Hospital; Developmental Neurology Branch, Medical Neurology Branch, NINCDS; Maryland Head Injury Foundation.

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Laboratory of Psychology and Psychopathology

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INSTITUTE AND LOCATION

NIMH, ADAMHA, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 4.0 | 0.8 | 3.2 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☒ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The aim of this project is to investigate the roles of event-related brain potentials, attention, and information processing and their interrelationships in the etiology, pathology, and prognosis of psychiatric and neurological disorders. Major emphasis is on the diagnostic specificity of disorders of attention and cognition and the identification of the specific aspects or stages of information processing underlying observed decrements in performance. Concurrently recorded event-related brain potentials and performance on cognitive tasks are used to define mechanisms of cognitive failure in subjects with diagnoses of seasonal affective disorder, schizophrenia, eating disorders, learning disorders, seizures, and closed head injury. Event-related brain potentials are also used to investigate the role of altered neurochemical mechanisms by comparing drug-induced electrophysiological and behavioral effects with those seen in the various disorders. Psychological correlates are investigated by relating the data to extensive neuropsychological, psychiatric, and personality measures as well as to performance on behavioral tasks.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02288-03 LPP

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Studies on Etiological Factors in Schizophrenia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | |
|---|---|---|
| PI: | Seymour S. Kety, M.D. | Senior Scientist, NIMH |
| Others: | Loring Ingraham, Ph.D. | Staff Fellow, LPP, NIMH |
| | Bjorn Jacobsen, M.D. | Assoc Prof Psychiatry, Univ. of Copenhagen |
| | Fini Schulsinger, M.D. | Prof. Psychiatry, Univ of Copenhagen |
| | Dennis Kinney, Ph.D. | Asst Prof Psychiatry, Harvard University |
| | Paul Wender, M.D. | Prof Psychiatry, Univ. of Utah |

COOPERATING UNITS *(if any)*

Psychological Institute, Copenhagen, Denmark; McLean Hospital, Belmont, Mass.; Harvard University; University of Utah.

LAB/BRANCH

Laboratory of Psychology and Psychopathology

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 2.0 | 2.0 | |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Studies of the occurrence of mental illness in families have been useful in identifying familial forms of the illnesses and in the development of hypotheses regarding the form and strength of genetic and environmental factors in etiology. Where these major variables are separated by the process of adoption, specific etiologic hypotheses can be tested separately and in combination. A total national sample of 14,500 adult adoptees in Denmark provides the basis of the main components of this research. The research this year has focused on 46 classical schizophrenic adoptees identified in the national sample with a comparable number of control adoptees with no history of mental illness. The remarkable population registers in Denmark permit the identification of the close biological and adoptive relatives of these adoptees. By search of mental hospital registers and ultimately by personal interviews, information on the psychiatric history and status of the relatives has been obtained. During the past year these interviews and other records have been used to obtain consensus diagnoses by two raters without knowledge of the relationship among relatives and adoptees. The first phase of the analysis has now been completed with results which confirm the findings on the first sample (restricted to Greater Copenhagen) that classical chronic schizophrenia occurs almost exclusively among the biological relatives of chronic schizophrenic adoptees and not in their adoptive relatives. A marginal syndrome which has been variously designated as latent or borderline schizophrenia or schizotypal personality was also found to be significantly more prevalent in the biological relatives of chronic schizophrenic adoptees, but was also more prevalent in the biological relatives of adoptees with other major mental disorders or marginal schizophrenia.

The study of mental disorder in the relatives of adoptees with affective disorder completed in the previous year has now been published.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

## NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02295-02 LPP

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Genetic Factors in Response to Alcohol

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | Connie C. Duncan, Ph.D. | Chief, Unit on Psychophysiology | LPP/NIMH |
| Co-PI: | Frances H. Gabbay, Ph.D. | Guest Researcher | LPP/NIMH |
| Others: | Allan F. Mirsky, Ph.D. | Chief | LPP/NIMH |
| | T. Peter Bridge, M.D. | Deputy AIDS Coordinator | ADAMHA |

COOPERATING UNITS *(if any)*

Department of Mental Hygiene, School of Hygiene and Public Health, Johns Hopkins University

LAB/BRANCH

Laboratory of Psychology and Psychopathology

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1.6 | 1.1 | 0.5 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of this project is to assess the relative contributions of genetic and environmental factors to alcohol drinking and response to alcohol challenge. The project is composed of two studies. In the first, 100 male monozygotic (MZ) and 100 male dizygotic (DZ) twin pairs will complete a questionnaire describing their alcohol and other drug use and a 28-day record of their alcohol intake. These data will permit estimation of the relative contributions of genetic and environmental factors to frequency and amount of alcohol consumption. In addition, self-reports of contact between cotwins will permit estimation of the importance of shared environment on cotwin similarities in alcohol drinking. Finally, comparison of the questionnaire estimates of alcohol consumption with those derived from the 28-day record will permit evaluation of the validity of the questionnaire method.

In the second study, 15 male MZ and 15 male DZ twin pairs will receive, in separate testing sessions, a placebo and two doses of alcohol (0.40 and 0.80 g/kg of 95% ethyl alcohol). The protocol will consist of electrophysiological measures (e.g., brainstem auditory evoked responses, resting EEG, and visual and auditory event-related potentials), self-reports of affect, and a measure of standing stability. The use of placebo and multiple doses of alcohol will permit conclusions about the effects of alcohol on information processing, response production, mood, and motor activity. The twin design will provide information on the relative contributions of genetic and environmental factors to variability in these measures in the drug-free state and following response to alcohol challenge. Finally, conclusions regarding the stability of the measures across time will be based on comparisons of baseline measures across the three sessions.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 MH 02404-01 LPP

PERIOD COVERED
July 21, 1987 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Psychophysiological Investigations of Preattentional and Attentional Function.

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | Bruno J. Anthony, Ph.D. | Senior Staff Fellow | LPP, NIMH |

COOPERATING UNITS *(if any)*

Department of Mental Hygiene, Johns Hopkins School of Hygiene and Public Health; Baltimore City Public Schools.

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INSTITUTE AND LOCATION
NIMH, ADAMHA, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| | | |

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☒ (a1) Minors
☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project applies a new methodology to examine dysfunction in preattentive and attentive mechanisms involved in the regulation of information processing within the central nervous system. Actions of these regulatory mechanisms are assessed through patterns of blink reflex modification, cardio-respiratory change and behavioral measures during simple two-stimulus paradigms. These measures are used to assess preattentive inhibitory and excitatory effects on sensory processing, the integration of different neural systems (sensory, motor and autonomic), and different components of attention including intensity, maintenance, breadth (focus or selectivity), and resistance to distraction. Reports of studies with normal infants, children and adults have been prepared and serve as the groundwork for clinical studies with groups exhibiting different types of regulatory dysfunction. Laboratory facilities and procedures have been developed, protocols have been designed, and pilot work is in its initial phases.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

**NOTICE OF INTRAMURAL RESEARCH PROJECT**

PROJECT NUMBER

Z01 MH 00672-22 LSES

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Social Psychological Correlates of Occupational Position

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: C. Schooler, Acting Chief, Laboratory of Socio-environmental Studies, NIMH

| | | | | |
|---|---|---|---|---|
| OTHER: | C. Schoenbach | Social Science Analyst | LSES | NIMH |
| | M. Kohn | Guest Researcher | LSES | NIMH |

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Socio-environmental Studies

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 5.00 | .50 | 4.50 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The object of this study is to assess the reciprocal effects of occupational conditions and psychological functioning (in particular, values, self-conceptions, social orientation, and intellectual flexibility). Structured interviews were conducted in 1964 with a sample of 3101 men, representative of all men employed in civilian occupations throughout the United States. The study was extended into a longitudinal study in 1974, with the reinterviewing of a randomly-selected one-fourth of the original sample, together with their wives and, where appropriate, one of their children. Replications of this research have been carried out in Poland and Japan.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

**NOTICE OF INTRAMURAL RESEARCH PROJECT**

PROJECT NUMBER

Z01 MH 00679-07 LSES

PERIOD COVERED

October 1, 1986 through September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Structural Equation Models in the Analysis of Data with Measurement Error

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | Ronald J. Schoenberg, Research Sociologist | LSES | NIMH |
| OTHER: | C. Schooler Acting Chief | LSES | NIMH |

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Socio-environmental Studies

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1.10 | 1.10 | |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of this work is to further develop the methods and techniques for the specification and estimation of the parameters of structural equation models of survey data that contain random and nonrandom measurement error. Included in this are methods for the identification of the models, estimation of the means of unobserved variables, the determination of model condition, and the treatment of polytomous variables.

| DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE<br>NOTICE OF INTRAMURAL RESEARCH PROJECT | PROJECT NUMBER<br>Z01 MH 00680-05 LSES |
|---|---|

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Work Experiences and the Deinstitutionalized Mentally Ill

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Elliot Liebow, Guest Researcher, LSES, NIMH

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Socio-environmental Studies

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The objective of this exploratory, participant observation study is to examine the work experience of the deinstitutionalized mentally ill over time and to seek out ways in which job characteristics, symptoms, and social relationships interact with one another to effect the course of recovery from psychiatric disorder and reintegration into the community. Field work was carried out with residents of halfway houses, participants in community-based psychosocial and transitional work programs, and with "unattached" deinstitutionalized men and women.

PHS 6040 (Rev 1/84)

GPO 914-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

# NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 MH 00681-01 LSES

PERIOD COVERED
October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Reciprocal Effects of Self-Esteem and Depression

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: M. Rosenberg, Guest Research, Laboratory of Socio-environmental Studies,NIMH

| | | | | |
|---|---|---|---|---|
| OTHER: | C. Schooler | Acting Chief | LSES | NIMH |
| | C. Schoenbach | Social Science Analyst | LSES | NIMH |

COOPERATING UNITS *(if any)*

None

LAB/BRANCH
Laboratory of Socio-environmental Studies

SECTION

INSTITUTE AND LOCATION
NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1.05 | .55 | .50 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Although low self-esteem has been shown to be associated with a number of non-pschotic disorders among children, adolescents, and adults, the causal connection among these variables has not been established. In order to do so, we plan to make use of a longitudinal data set. This is the Youth in Transition study, a five-wave national probability sample of adolescents. Through the use of instrumental variables and structural equation models, we will seek to specify the reciprocal effects of global self-esteem and a number of mental health and behavioral variables.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00682-01 LSES

PERIOD COVERED
October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Environmental Determinants of Cognitive Functioning

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | L. Caplan, Staff Fellow | LSES | NIMH |
| OTHER: | C. Schooler, Acting Chief | LSES | NIMH |

COOPERATING UNITS *(if any)*

None

LAB/BRANCH
Laboratory of Socio-environmental Studies

SECTION

INSTITUTE AND LOCATION
NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1.60 | 1.35 | .25 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of this study is to investigate the effects of task complexity on cognitive functioning. Subjects were trained to use a computer program under different conditions of complexity. After training, the following were assessed: 1) knowledge structure development, 2) flexibility of problem solving, and 3) planning ability.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00424-12 LCB

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Biologically Active Peptides in the Brain

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.s

Michael J. Brownstein, Chief, Laboratory of Cell Biology, NIMH
T. Bonner, Special Expert, Laboratory of Cell Biology, NIMH
C. Gerfen, Sr. Staff Fellow, Laboratory of Cell Biology, NIMH
M. Palkovits, Visiting Scientist, Laboratory of Cell Biology, NIMH
W. S. Young, Sr. Staff Fellow, Laboratory of Cell Biology, NIMH
(see attached)

COOPERATING UNITS *(if any)* Univ. Zuerich; Tulane Univ; Neurol.Sci.Inst., Portland; MD NIDDKD; CNG NIMH; BG NHLBI; ERR CH; Tufts U. Med. Sch; Westminster Hosp., London; LVC NCI; LMG NINCDS; BPB NIMH; Karolinska Inst; LNC NINCDS

LAB/BRANCH

Laboratory of Cell Biology

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

| | | |
|---|---|---|
| TOTAL MAN-YEARS:<br>10 | PROFESSIONAL: | OTHER:<br>0.0 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects
  ☐ (a1) Minors
  ☐ (a2) Interviews
☐ (b) Human tissues
☒ (c) Neither

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

We have continued to study the organization and development of peptidergic and non-peptidergic neurons in the central nervous system and periphery, biosynthesis of biologically active peptides, factors that regulate peptide secretion, and receptors and their second messenger systems.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

**NOTICE OF INTRAMURAL RESEARCH PROJECT**

PROJECT NUMBER

Z01 MH 02302-02 LCB

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Biochemical Studies on Myelin Basic Protein

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

R. E. Martenson

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Cell Biology

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

| | | |
|---|---|---|
| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project has been discontinued because the principal investigator left the Laboratory of Cell Biology.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00422-16 LCB

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Neuropharmacology of Circadian Rhythms

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | M. Zatz | Section Chief | SBP,LCB,NIMH |
| Others: | N. Harrison | Visiting Fellow | LNP,NINCDS |
| | M. Warden | Biologist | LCB,NIMH |

COOPERATING UNITS *(if any)*

LNP, NINCDS

LAB/BRANCH

Laboratory of Cell Biology

SECTION

Section on Biochemical Pharmacoloy

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1.9 | 1.0 | 0.9 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Circadian rhythms and environmental lighting regulate a number of endocrine and behavioral functions. Dispersed chick pineal cells remain rhythmic and responsive to light in culture. Photosensitivity appears to reside in the same cells as melatonin production. The mechanisms of phototransduction appear to differ from those in retinal rod cells. Light, membrane potential, norepinephrine, cyclic AMP, and calcium channels regulate melatonin rhythms in these cells.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

**NOTICE OF INTRAMURAL RESEARCH PROJECT**

PROJECT NUMBER

Z01 MH 00429-08 LCB

PERIOD COVERED

October 1, 1986 - September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Biochemistry of Membranes

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | M. Zatz | Section Chief | SBP, LCB, NIMH |
| Others: | L.C. Mahan | Staff Fellow | LCB, NIMH |

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Cell Biology

SECTION

Section on Biochemical Pharmacology

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 0.2 | 0.1 | 0.1 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

1.) Previous work explored the mechanisms by which lithium causes ACTH secretion from anterior pituitary tumor cells. Departure of one of the investigators and technical difficulties have delayed further work on this problem.

2.) Previous work demonstrated the acylation of rhodopsin by long chain fatty acids in vivo and in vitro. Further work on this problem waits identification of the opsin mediating photoreception in cultured chick pineal cells which will provide a model system for the exploration of the role of this new class of posttranslational modification in receptor function.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00434-06 LCB

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Molecular Mechanisms of Receptor-Mediated Signal Transduction

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | Julius Axelrod | Guest Researcher | LCB,NIMH |
| Others: | R. Burch | Guest Researcher | LCB,NIMH |
| | B. Conklin | Guest Researcher | LCB,NIMH |
| | C. Felder | Staff Fellow | LCB,NIMH |
| | C. L. Jelsema | Guest Researcher | LCB,NIMH |
| | A. D. Ma | Guest Researcher | LCB,NIMH |
| | A. L. Ma | Biologist | LCB,NIMH |
| | L. Mahan | Staff Fellow | LCB,NIMH |

COOPERATING UNITS *(if any)*

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Laboratory of Cell Biology

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 5.0 | 5.0 | 0 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

GTP-regulatory proteins, in particular transducin, mediate light-induced stimulation of phospholipase A$_2$ and C (PLA$_2$, PLC) in rod outer segments (ROS) of bovine retina. Studies using G protein-specific agents, cholera toxin and pertussis toxin, in both light and dark-adapted ROS suggest a dual role for G proteins in both activation and inhibition of PLA$_2$ and PLC. $\beta\gamma$ subunits of transducin stimulated PLA$_2$ while $\alpha$ subunits were inhibitory. Both $\alpha$ and $\beta\gamma$ subunits of transducin stimulated PLC, possibly through the inhibition of a inhibitory G protein. In addition to light, stimulation of PLA$_2$ and PLC by other retinal neurotransmitters, in particular dopamine and somatostatin has been characterized. Isolated $\alpha$ subunits from G$_s$, G$_i$, G$_o$ and transducin were phosphorylated in vitro by cAMP-dependent protein kinase and protein kinase C. Phosphorylated subunits were altered in their ability to stimulate phospholipase activity and this may represent a biochemical mechanism of regulation of G protein-mediated pathways. In retina from Xenopus laevis, both somatostatin and dopamine inhibit the circadian rise in N-acetyl transferase (NAT), the rate limiting enzyme in melatonin synthesis. These effects are mediated by G proteins although through different transduction mechanisms. Somatostatin, acts through a non-cAMP dependent mechanism. Receptors for somatostatin are regulated by Na$^+$ and GTP and co-localize with G proteins, in particular G$_o$, by autoradiographic and immunocytochemical analyses respectively. In addition, the ability to immunocytochemically detect G protein subunits is markedly altered during peak periods of circadian activity.

Activation of PLA$_2$ and PLC by bradykinin has been shown to occur through distinct G proteins in Swiss 3T3 cells. Activation of PLA$_2$ occurs via a pertussis toxin-insensitive G protein. Evidence to support the existence of two distinct bradykinin receptor subtypes coupled to the activation of phospholipases was obtained.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02385-01 LCB

PERIOD COVERED

October 1, 1986 - September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Genetic Control of Cell Differentiation, Growth and Transformation

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | H. Okayama | Visiting Scientist | LCB, NIMH |
| Others: | M. Kawaichi | Visiting Associate | LCB, NIMH |
| | M. Eiden | Guest Researcher | LCB, NIMH |
| | A. Masuda | Visiting Fellow | LCB, NIMH |
| | C. Chen | Biologist | LCB, NIMH |
| | N. Nukiwa | Guest Researcher | LCB, NIMH |

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Cell Biology

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 3.4 | | |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

A highly efficient transfection protocol and a plasmid vector for the construction and delivery into mammalian cells of cDNA expression libraries have been developed. Many commonly used fibroblastic cell lines are stably transfected at frequencies of >10% with the cDNA cloning vector that incorporates a neo selectable marker. The system permits cloning of cDNAs on the basis of their function expressed in mammalian cells.

The majority of human cancers seem to be induced by a recessive mechanism (recessive oncogenes). To clone such a novel type oncogene, nitroso methylurea-transformed BHK cells were transfected with a cDNA expression library constructed with the new vector and mRNA prepared from primary human fibroblast cells. After neo selection and morphological screening, two flat revertants that were unable to grow in soft agar were isolated. In secondary transfection with the genomic DNA prepared from one of the two revertants, the flat phenotype co-transmitted with neo resistance. The cDNA that induces flat reversion is being recovered in E. coli for molecular cloning and characterization.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02386-01 LCB

PERIOD COVERED

October 1, 1986 through September 30, 1987.

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Neuropeptide Secretion, Synthesis and Action in Neural, Endocrine and Immune Cells

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: Lee E. Eiden Pharmacologist LCB, NIMH

See Attached

COOPERATING UNITS *(if any)*

U. Strasbourg; D.C. V.A.; LDN, NICHHD; NIAAA; U. Innsbruck, UCSF; A. Einstein Coll. Med.; Merrell-Dow Res. Inst.; Case Western Reserve; USUHS

LAB/BRANCH

Laboratory of Cell Biology

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

| | | |
|---|---|---|
| TOTAL MAN-YEARS:<br>6 | PROFESSIONAL: | OTHER: |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

We are examining the molecular mechanisms of neuropeptide secretion, neuropeptide expression and biosynthesis and neuropeptide interactions with their receptors in the developing and mature neuroendocrine system. We are attempting to understand the structural features of peptides and proteins that confer molecular specificity on these three processes. We hope to characterize and develop pharmacological agents that mimick this specificity.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02387-01 LCB

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Structural Analysis of the CD4/HIV Ligand/Receptor Dyad

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | Lee E. Eiden | Pharmacologist | LCB, NIMH |
| Others: | Jeff Lifson | Director of Immunology | Genelabs, Inc. |
| | Pat Padgett | Chemist | LMG, NINCDS |
| | Pete Nara | Biologist | FCRF, NCI |
| | Kou Hwang | Chemist | Genelabs, Inc. |
| | Blair Fraser | Chemist | FDA |

COOPERATING UNITS *(if any)*

Genelabs, Inc., Frederick Cancer Research Facility, FDA
LMG, NINCDS

LAB/BRANCH

Laboratory of Cell Biology

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1 | | |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Peptide fragments of the CD4 antigen were synthesized and tested for antiviral activity. A derivatized 19 amino acid fragment of the molecule inhibits HIV-mediated T-lymphocyte fusion and HTLV-IIIB infection of CEM cells, with an ED50 of 10-100 µM in the presence of approximately 250TCID$_{50}$ of the virus. The peptide is ineffective to block T-cell infection by HTLV-I, or to block other CD4-dependent cellular responses, e.g. the mixed lymphocyte reaction.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 MH 02396-01 LCB

PERIOD COVERED
October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Mechanical, Thermal and Optical Signs Of Excitation In the Nervous System

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

| | | | |
|---|---|---|---|
| PI: | Ichiji Tasaki | Chief, Unit of Neurobiology | LCB, NIMH |
| Others: | Paul M. Byrne | Biomedical Eng. Technician | LCB, NIMH |
| | Michio Masumura | Visiting Fellow<br>(appointed Jan. 1987) | LCB, NIMH |

COOPERATING UNITS (if any)

LAB/BRANCH

SECTION

INSTITUTE AND LOCATION
NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 2.5 | 1.5 | 1 |

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

We continued and expanded our investigation of non-electrical signs of excitation processes in the nervous system. Using isolated spinal cord preparations of the bullfrog and newborn rat, we found that afferent nerve impulses arriving at the spinal cord evoke a rapid rise in the temperature of the cord. A thorough examination of the observed temperature rise has indicated that transmission of nerve impulses across the synapses at the terminals of the sensory fibers is accompanied by generation of a considerable amount of heat in the substantia gelatinosa. This discovery of the "thermal response" of the spinal cord has given us a new, useful tool for studying the effects of various chemicals on synaptic transmission. We also examined excitation processes in the bullfrog retina by using our thermal detectors and piezoelectric sensors. We found that the photoreceptors in the dark-adapted retina are capable of releasing thermal energy which is more than one million times as large as the energy of the light pulse used for stimulation. Furthermore, we found it possible to analyze the processes of synaptic transmission in the retina by taking its mechanical responses as an index.

This is a continuation of Project #Z01 MH 00981 LNP.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00881-31 LCM

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Intermediary Energy Metabolism in Mammalian Brain

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| P.I.: | Elaine E. Kaufman | Research Chemist | LCM, NIMH |
| Others: | Thomas Nelson | Medical Officer (Research) | LCM, NIMH |

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Cerebral Metabolism

SECTION

Section on Developmental Neurochemistry

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 2.7 | 1.2 | 1.5 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This report will describe work carried out in this laboratory which resulted in the discovery and characterization of a mammalian mitochondrial transhydrogenase, an enzyme capable of transferring hydrogens from specific hydroxyacids to equally specific ketoacids. This work suggests new catabolic pathways for L-β-hydroxybutyrate, γ-hydroxybutyrate and α-ketoglutarate and may explain the origin of the elevated levels of certain hydroxyacids found in patients with specific organic acidemias.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00882-20 LCM

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Studies on Regional Cerebral Circulation and Metabolism

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| P.I.: | Louis Sokoloff | Chief, Lab. Cerebral Metabolism | LCM, NIMH |
| Others: | Charles Kennedy | Guest Researcher | LCM, NIMH |
| | Thomas Nelson | Medical Officer (Research) | LCM, NIMH |
| | Carolyn B. Smith | Research Chemist | LCM, NIMH |
| | Gerald A. Dienel | Senior Staff Fellow | LCM, NIMH |
| | Nancy Cruz | Biologist | LCM, NIMH |
| | Nancy Eng | Chemist | LCM, NIMH |

COOPERATING UNITS *(if any)*

Theoretical Statistics & Mathematics Branch, NIMH (C.S. Patlak & K.D. Pettigrew); NINCDS, NIH (I. Kopin); NIDA, ARC, Baltimore, Maryland (L. Porrino).

LAB/BRANCH

Laboratory of Cerebral Metabolism

SECTION

Section on Developmental Neurochemistry

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 9.50 | 6.00 | 3.50 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The deoxyglucose method for the quantitative determination of rates of local glucose consumption in the discrete functional and structural components of the brain of conscious or anesthetized laboratory animals was developed in this laboratory over 10 years ago. In this method [$^{14}$C]deoxyglucose is employed as a tracer for glucose flux through the hexokinase step; the product, [$^{14}$C]deoxyglucose-6-phosphate, is measured by quantitative autoradiography. The method continues to be used to study alterations in local energy metabolism in a variety of physiological, pharmacological and a limited number of pathological states. Its suitability to a wider range of pathologic conditions is being extended and special time constraints which may be present in the method's adaptation for use in human subjects with [$^{18}$C]fluorodeoxyglucose and PET have been examined.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00887-10 LCM

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

The Extended Visual System of the Macaque Monkey

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| P.I.: | Charles Kennedy | Guest Researcher | LCM, NIMH |
| Others: | Louis Sokoloff | Chief | LCM, NIMH |

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Cerebral Metabolism

SECTION

Section on Developmental Neurochemistry

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 2.0 | 1.25 | 0.75 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Although the project began with its focus on mapping the visually responsive cortical areas, the experiments also permit an analysis of the sensory-motor system. Normal control monkeys with their visual pathways intact responded to the visual cues by pressing a lever with one hand. This involved an asymmetrical pattern of local glucose utilization in brain involving a wide expanse of cortical and sub-cortical structures. An analysis of the pattern of asymmetry provides new information with respect to the localization sensory-motor function. The data obtained to date indicate that a much larger portion of brain regions are unilaterally activated on unimanual activity than has been appreciated previously.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00889-08 LCM

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

A Method for the Determination of Local Rates of Protein Synthesis in Brain

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| P.I.: | Carolyn B. Smith | Research Chemist | LCM, NIMH |
| Others: | Louis Sokoloff | Chief | LCM, NIMH |
| | Christina Eintrei | Visiting Fellow | LCM, NIMH |
| | Charles Kennedy | Guest Researcher | LCM, NIMH |
| | Mortimer Mishkin | Chief | LN, NIMH |
| | Richard Nakamura | Guest Researcher | LN, NIMH |

COOPERATING UNITS *(if any)*

Department of Neurosurgery, Univ. of Texas (M. Kadekaro); Dept. of Obstetrics & Gynecology, Univ. of Florida (R. Abrams); Department of Neurosurgery, SUNY (D. Dow-Edwards)

LAB/BRANCH

Laboratory of Cerebral Metabolism

SECTION

Section on Developmental Neurochemistry

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 2.8 | 1.6 | 1.2 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

A method has been developed for the estimation of local rates of protein synthesis in brain in vivo. The method is based on the use of L-[$^{14}$C]leucine as a tracer for the incorporation of leucine into protein. Six kinetic models for the behavior of leucine in brain have been designed. By mathematical analysis of the kinetics of exchange of the amino acid between plasma and the tissue pool(s) and its incorporation into protein, equations have been derived for each model that define the rate of amino acid incorporation into protein in terms of the time course of plasma-specific activity, final tissue concentration of $^{14}$C, and experimentally determined kinetic constants. Tissue concentrations of $^{14}$C are determined by quantitative autoradiography. Experiments have been carried out to test the validity of the various models and to determine the kinetic constants to be used in the operational equation.

Studies of the effects of normal development, sleep, anesthesia, electrical stimulation and hypothyroidism on cerebral protein synthesis have been undertaken in order to examine the potential usefulness of the leucine method.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

**NOTICE OF INTRAMURAL RESEARCH PROJECT**

PROJECT NUMBER

Z01 MH 00903-10 LCM

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Purification and Identification of Brain Proteinases and their Cleavage Products

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| P.I.: | Gladys E. Deibler | Research Chemist | LCM, NIMH |
| Others: | Marian W. Kies | Chemist | LCM, NIMH |
| | Audrey Stone | Guest Researcher | LDMI, NICHHD |

COOPERATING UNITS *(if any)*

Multiple Sclerosis Research Center; Dept. of Neurology, Georgetown University (J. Richert)

LAB/BRANCH

Laboratory of Cerebral Metabolism

SECTION

Section on Developmental Neurochemistry

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 2.5 | 1.5 | 1.0 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Our exhaustive review of the many papers on brain proteinases led us to choose calcium activated neutral proteinases (CANP I, II and III) as the brain enzymes that we will investigate. CANP I is located in the neurons, CANP II is located in the glia cells, and CANP III has not been associated with a particular structure. Presently, we are developing the specific analytical methods needed to extract, purify, characterize and assay the CANP's.

Our previous investigation of human myelin basic protein (HBP) led to the identification and characterization of a new form of HBP with a molecular weight of 17.2 kDa and highly purified HBP-component 1, the unmodified 18.5 kDa protein. Highly purified HBP-component 1 was cleaved with thrombin and the resulting two peptides (1-97 & 98-170) were purified and characterized. HBP-component 1, 17.2 kDa HBP and the two thrombic peptides (residues 1-97 & 98-170) were used in collaboration with Dr. John Richert, Dept. of Neurology, Georgetown University. Forty myelin basic protein-reactive T cell clones were isolated from a multiple sclerosis patient and used to identify human T cell recognition sites on the HBP molecule. At least three sites have been identified: One in the N-terminal half of the molecule (residues 1-97), one in the C-terminal (residues 98-170), and one which spans residues 97-98.

In collaboration with Dr. Audrey Stone, we have completed the investigation on the role of phosphorylation on the conformational adaptability of bovine myelin basic protein (MBP). The limited digestion of MBP-components 2 + 3 yielded a mono-phosphorylated component which was phosphorylated only at threonine 97. From the circular dichroism of this homogeneous mono-phosphorylated MBP, we determined that the β-structure of this protein was increased by 7%, when compared with MBP-component 1. The single phosphorylation on threonine 97 produced a change in the macrostructure of the protein involving about 12 amino acid residues.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

**NOTICE OF INTRAMURAL RESEARCH PROJECT**

PROJECT NUMBER

Z01 MH 02216-04 LCM

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Metabolic Mapping of the Brain during Rewarding Self-Stimulation

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| P.I.: | Linda J. Porrino | Guest Researcher | LCM, NIMH |
| Others: | Louis Sokoloff | Chief | LCM, NIMH |

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Cerebral Metabolism

SECTION

Section on Developmental Neurochemistry

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 2.00 | 1.5 | 0.5 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The deoxyglucose method is being used to study alterations in local cerebral glucose utilization resulting from rewarding electrical brain self-stimulation to discrete brain sites as well as resulting from the administration of drugs of abuse. By mapping metabolic activity in rats under these conditions, information can be obtained about those areas of the brain involved in motivation and reinforcement.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02217-04 LCM

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Plasticity in the Developing Monkey Visual System

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| P.I.: | Carolyn B. Smith | Research Chemist | LCM, NIMH |
| Others: | Louis Sokoloff | Chief | LCM, NIMH |
| | Karen D. Pettigrew | Res. Math. Statistician | TSMB, NIMH |
| | Susan Herdman | Guest Researcher | LCM, NIMH |

COOPERATING UNITS *(if any)*

Department of Neurology, Johns Hopkins Medical School, Baltimore, MD (R. Tusa)

LAB/BRANCH

Laboratory of Cerebral Metabolism

SECTION

Section on Developmental Neurochemistry

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 0.8 | 0.5 | 0.3 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The postnatal development of the central visual pathways depends on the quality of the visual environment. During the critical period in the primate visual system environmental manipulation can modify the physiological properties of visual cortical cells. The purpose of this project is to study the underlying biochemical events that imbue the nervous system with the property of plasticity. Protein synthesis is a biochemical process which is involved in bringing about changes in morphology, adjustments in growth rates, and remodeling and maintenance of structures. We have, therefore, used the $[^{14}C]$leucine method to study the relationships between local plastic changes which occur in the developing monkey visual system and local rates of protein synthesis.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

# NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02220-04 LCM

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Regional Biochemical Changes in the Normal Aging Brain

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

| | | | |
|---|---|---|---|
| P.I.: | Carolyn B. Smith | Research Chemist | LCM, NIMH |
| Others: | Louis Sokoloff | Chief | LCM, NIMH |
| | Ernesta Palombo | Visiting Fellow | LCM, NIMH |

COOPERATING UNITS (if any)

Department of Physiology-Anatomy, University of California, Berkeley, CA
(M. C. Diamond)

LAB/BRANCH

Laboratory of Cerebral Metabolism

SECTION

Section on Developmental Neurochemistry

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 0.5 | 0.4 | 0.1 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Studies have been carried out on the effects of aging on cerebral protein synthesis and glucose utilization in rats. With the application of local methods developed in this Laboratory, discrete regions of the brain can be examined in normal conscious animals. The regional changes in glucose utilization indicate that entire sensory pathways are affected by the aging process. The fact that similar changes are found in the same pathways with respect to protein synthesis suggests that some of these changes reflect an adaptation of the nervous system to a chronic lack of input. Our findings of age-dependent decreases in glucose utilization in the striatum have been followed up with studies of the effects of aging on the metabolic responsiveness to the dopaminergic agonist apomorphine.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02308-02 LCM

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Growth and Development of Dopaminergic Neurons

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| P.I.: | Bernard F. Driscoll | Research Biologist | LCM, NIMH |

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Cerebral Metabolism

SECTION

NIMH, Bethesda, Maryland 20892

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1.5 | 1.0 | 0.5 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Development of central nervous system pathways involves the action of soluble factors on target cells and interactions between various cell types. One of the best defined CNS pathways is the nigrostriatal pathway. To examine events involved in the formation of this pathway, development of dopaminergic neurons from the embryonic rat mesencephalon was examined in dissociated cell cultures.

Cells were grown in serum-free medium or serum-containing medium in the presence or absence of the basement membrane component, laminin. Mesencephalic cells were obtained from embryonic day 13 to embryonic day 15 rat brains; cells from other regions were obtained from embryonic or postnatal rat brains at times when subsequent in vitro development was shown to be optimal. Development of the dopaminergic neurons in the mesencephalic cultures was determined by uptake of exogenous, labelled dopamine.

Mesencephalic dopaminergic neurons grown alone developed vigorously in culture for 9 days. After this time development ceased. In contrast, if mesencephalic neurons were grown in the presence of cells from other brain regions, the cultures continued to develop to day 20 or day 27. Glial cells from these other brain regions appear to be important for the continued development of the mesencephalic neurons. There also appeared to be a later stage of development or cell survival that was dependent on the presence of specific target cells in the culture. Striatal neurons are the normal in vivo target for most of the mesencephalic dopaminergic neurons. Cells from the striatum provided optimum in vitro conditions for development of the dopaminergic neurons.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02307-02 LCM

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Role of Proteinases in Production and Control of Neuropeptides

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

| | | | |
|---|---|---|---|
| P.I.: | Marian W. Kies | Chemist | LCM, NIMH |
| Others: | Gladys E. Deibler | Research Chemist | LCM, NIMH |

COOPERATING UNITS (if any)

None

LAB/BRANCH

Laboratory of Cerebral Metabolism

SECTION

Section on Developmental Neurochemistry

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| | | |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This project has temporarily been postponed due to the prolonged absence of the Principal Investigator on account of illness. It is planned that the research will resume the beginning of FY 1988.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

**NOTICE OF INTRAMURAL RESEARCH PROJECT**

PROJECT NUMBER
Z01 MH 00507-05 LCM

PERIOD COVERED
October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Clinical Brain Imaging

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Robert M. Cohen, M.D., Ph.D., Chief, CBI, LCM, NIMH

COOPERATING UNITS *(if any)*

Clinical Neuroscience Branch, NIMH (D. Pickar); Clinical Center, NIH (C. Channing and R. Carson); Child Psychiatry Branch, NIMH (A. Zametkin)

LAB/BRANCH
Laboratory of Cerebral Metabolism

SECTION
Section on Clinical Brain Imaging

INSTITUTE AND LOCATION
National Institute of Mental Health
9000 Rockville Pike, Bethesda, MD 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 8.5 | 4.5 | 4.0 |

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The major areas of effort in this project have been (1) to develop new tracers or other approaches for the study of neurotransmitter function in normal and abonormal physiology; and (2) to apply what tracer methodologies we have available to the study of neuropsychiatric disorders. To these ends, the following achievements are notable. A series of studies of [18F]-cyclofoxy have been completed in baboons that delineate its usefulness as a measure of opiate receptor avidity. An application for its use in humans has been submitted to the Food and Drug Administration. We found that we could successfully apply PET measurement of glucose metabolism to determine biological determinants of attention as we observed for what we believe to be the first time a direct relationship between the metabolic activity of a brain region, the mid-prefrontal cortex and quantitative measures of the accuracy of ongoing performance of auditory discrimination in normals. In patients with schizophrenia, even those who performed as well as normals, the metabolic rate in the middle prefrontal cortex was found to be significantly lower than normal and unrelated to performance. Furthermore, preliminary analysis suggests that medicated patients with schizophrenia demonstrate a similar relationship between the middle prefrontal cortex and performance as normal controls. The findings point to a role of the mid-prefrontal cortex and its dopamine neurotransmitter pathway input in sustained attention and to dysfunction of this region and of its dopamine modulation in some patients with schizophrenia.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

## NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02296-02 LCM

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

In Vivo Tomographic Imaging of Dopaminergic Systems and their Turnover

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

C. C. Chiueh Pharmacologist LCM NIMH

COOPERATING UNITS *(if any)*

Nuclear Medicine, CC, NIH (S. Larson); Office of the Director, IRP, NINCDS (I. Kopin); Dept. of Nuclear Medicine, McMaster Univ. Medical Centre, Hamilton, Ontario, Canada (G. Firnau)

LAB/BRANCH

Laboratory of Cerebral Metabolism

SECTION

Section on Clinical Brain Imaging

INSTITUTE AND LOCATION

National Institute of Mental Health, 9000 Rockville Pike Bethesda, MD 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 3.0 | 2.5 | 0.5 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

We have established a neurochemical basis for the use of purified [F-18]-labeled L-6-F-dopa as a presynaptic imaging ligand for brain dopaminergic neurons. A potential clinical use of this PET imaging ligand for brain dopamine in determining degrees of brain damage in parkinsonian patients was demonstrated in this study by using the MPTP-induced primate model of parkinsonism. Despite a high background activity due to contamination, we were able to image striatal dopaminergic neurons in living monkeys by using the Scanitronix PET scanner at the NIH Clinical Center. The striatal [F-18]-labeled dopaminergic activity was diminished in the monkeys that received a partially purified [F-18]-labeled 6-F-dopa and indicates a need to purify further this PET imaging ligand prior to the application of this 6-F-dopa/PET procedure in humans. By using animal models of parkinsonism, we have also evaluated a new SPECT imaging ligand for D2 dopamine receptors, [I-123]-labeled IBZM (3-iodobenzylamide derivative). It has been shown that IBZM specifically binds to D2 dopamine receptors in the brain and is displaceable by both agonists and antagonists of the D2 dopamine receptor. The in vivo imaging of the D2 dopamine receptors in the caudate nucleus, nucleus accumbens, olfactory tubercle and the kidney were obtained within thirty minutes following the administration of the radioactively labeled IBZM. A denervation induced decrease in dopaminergic fibers and increase in D2 dopamine receptors in the basal ganglia of experimental parkinsonian animals have been imaged by using these pre- and post-synaptic imaging ligands. Thus, this pre-clinical study has demonstrated potential clinical uses of these imaging ligands for studying in vivo the dopaminergic activities in patients with neuropsychiatric or Parkinson disorders.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00931-14 LGCB

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Characteristics and Regulation of S-Adenosylhomocystein Hydrolase

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| P.I. | P. S. Backlund, Jr. | Senior Staff Fellow | LGCB NIMH |
| | R. R. Aksamit | Research Chemist | LGCB NIMH |
| | G. L. Cantoni | Chief, Laboratory of General and Comparative Biochemistry | LGCB NIMH |

COOPERATING UNITS *(if any)*

Department of Biochemistry, Toyama Medical and Pharmaceutical University, Toyama, Japan

LAB/BRANCH

Laboratory of General and Comparative Biochemistry

SECTION

Section on Proteins

INSTITUTE AND LOCATION

NIMH, ADAMHA, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 3.5 | 2 | 1.5 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

S-adenosylhomocysteine hydrolase plays a critical role in regulating AdoMet-dependent methylations in eukaryotic cells by regulating the ratio of AdoMet/AdoHcy. Several approaches are being used to determine the structure and function of this enzyme.

1) Structure Determination: The enzyme has been purified from rat liver, and cloned from a rat liver cDNA library. The amino acid sequence was determined and a putative NAD binding site identified. The rat liver enzyme has been expressed in E. coli and site-directed mutagenesis is in progress to determine the function of specific amino acid residues. Conformational changes for active and inactive forms of the enzyme have been examined by fluorescence, and circular dichroism.

2) Ligand Binding and Kinetic Properties: The role of NAD, nucleotide, and cAMP binding in regulating the catalytic activity has been studied, and photoaffinity ligands are being used to label the binding sites. A large number of adenosine and adenosylhomocysteine analogs have been examined for their ability to function as inhibitors and/or substrates of the enzyme.

3) Biological Effects of Inhibitors: In vivo these adenosine analogs can form very potent and specific inhibitors of transmethylation reactions, and these inhibitors have a wide range of biological activities, including antiviral activity against several RNA and DNA viruses, inhibition of leukocyte chemotaxis, and stimulation of cell differentiation.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

**NOTICE OF INTRAMURAL RESEARCH PROJECT**

PROJECT NUMBER

Z01 MH 00936-23 LGCB

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Homocystinuria: Methionine Metabolism in Mammals

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

S.H. Mudd Chief, Section on Alkaloid Biosynthesis LGCB NIMH

COOPERATING UNITS *(if any)* William Gahl Human Genetics Branch Child Health and Human Dev.
James Finkelstein, Va Hospital and George Washington Univ., Washington, D.C.
Alfred Tangerman, Dept of Medicine, St. Radboud Univ. Hospital., Nijmegen, The Netherlands

LAB/BRANCH

Laboratory of General and Comparative Biochemistry

SECTION

Section on Alkaloid Biosynthesis

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 0.1 | 0.1 | 0 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Studies of a 31-year-old man with proven partial deficiency of hepatic methionine adenosyltransferase (MAT) activity have been continued. Identified abnormal metabolites in his bodily fluids, urine, and/or breath include: L-methionine-d-sulfoxide, 4-methylthio-2-oxo-butyrate, 3-methylthiopropionate, dimethylsulfide, and a mixed disulfide $CH_3S$-SX, the structure of which is still under investigation. Balance studies have permitted calculation of the fluxes of methyl- and sulfur-containing compounds and shown that: In spite of the deficient activity of hepatic MAT, the patient forms a normal amount of the product of this enzyme, S-adenosylmethionine (SAM). In spite of the normal rate of formation of SAM, the patient does not convert methionine sulfur to sulfate at a normal rate. In spite of his high body load of methionine, the patient conserves methionine by $N^5$-methyltetrahydrofolate-dependent methylation of homocysteine. The later observations are explained in terms of the regulatory effects of SAM on cystathionine synthase and methylenetetrahydrofolate reductase. In the presence of 20- to 50-fold elevations of methionine, the transamination pathway metabolizes about 20% of the normal methionine intake of this patient, although the transamination pathway is clearly not sufficiently active to prevent the accumulation of methionine.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

**NOTICE OF INTRAMURAL RESEARCH PROJECT**

PROJECT NUMBER
Z01 MH 00940-06 LGCB

PERIOD COVERED
October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Methionine Biosynthesis in Higher Plants

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

| | | |
|---|---|---|
| A.H. Datko | Biologist | LGCB NIMH |
| S.H. Mudd | Chief, Section on Alkaloid Biosynthesis | LGCB NIMH |

COOPERATING UNITS (if any)
R. Aksamit, LGCB NIMH

LAB/BRANCH
Laboratory of General and Comparative Biochemistry

SECTION
Section on Alkaloid Biosynthesis

INSTITUTE AND LOCATION
NIMH, ADAMHA, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1.7 | 1.7 | 0 |

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Investigation of the pathways for biosynthesis of phosphatidylcholine has been extended to two plants in addition to the Lemna previously studied, and to rat liver and hepatoma cells. Especial attention was focussed upon the role of phosphoethanolamine derivatives by use of methods which had demonstrated the participation of such derivatives in Lemna. Surprisingly, each of the plant tissues uses different steps to carry out the methylation reactions involved, although methylation of phosphoethanolamine appears to be the committing step common to each plant. Choline, or a metabolite thereof, markedly down-regulates entry of methyl groups into the network of methylated ethanolamine derivatives in each of the three tissues.

Rat liver uses a pathway which is again different in which all three methylations take place at the phosphatidyl-base level. In hepatoma cells it was demonstrated that entry of methyl groups into this pathway is regulated also by the availability of choline.

|  |  |
|---|---|
| DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE<br>NOTICE OF INTRAMURAL RESEARCH PROJECT | PROJECT NUMBER<br>Z01 MH 00942-06 LGCB |

PERIOD COVERED
October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less Title must fit on one line between the borders.)
Biochemical Reactions in Mammalian Cell Chemotaxis

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

| | | | |
|---|---|---|---|
| P.I. | R. R. Aksamit | Research Chemist | LGCB NIMH |
| | P. S. Backlund, Jr. | Senior Staff Fellow | LGCB NIMH |
| | G. L. Cantoni | Chief, Laboratory of General and Comparative Biochemistry | LGCB NIMH |

COOPERATING UNITS (if any)
Office of Biologics, FDA; Molecular Pathophysiology Section, NIDDJ;
Department of Biochemistry and Pharmacology, University of Glasgow, Scotland

LAB/BRANCH
Laboratory of General and Comparative Biochemistry

SECTION
Section on Proteins

INSTITUTE AND LOCATION
NIMH, ADAMHA, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER. |
|---|---|---|
| 1 | 0.5 | 0.5 |

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Chemotaxis by the RAW264 mouse macrophage cell line was inhibited by 3-deazaadenosine but not by 3-deazaaristeromycin. A search for biochemical reactions inhibited by 3-deazaadenosine but not by 3-deazaaristeromycin has revealed that only one reaction, the synthesis of a small number of proteins identified after separation by two-dimensional polyacrylamide gel electrophoresis, has the necessary inhibitor specificity for involvement in the 3-deazaadenosine-sensitive step of chemotaxis. A study with several adenosine analogs showed a correlation between inhibition of chemotaxis and inhibition of the synthesis of a common subset of proteins. These analogs also inhibited the synthesis of polyadenylated mRNA, leading us to postulate that incubation of cells with 3-deazaadenosine inhibits methylation reaction(s) required for the formation of functional mRNA coding for one or more proteins required for chemotaxis.

Experiments to identify attractant-specific proteins have been limited because chemically defined attractants for RAW264 cells have not been available. This problem has been overcome by the isolation of a stable cell hybrid from a fusion between human leukocytes and a thioguanine-resistant RAW264 cell line. The hybrid expressed functional genes for chemotaxis to fMet-leu-phe, a commercially available synthetic attractant. Binding of fMet-leu-phe to hybrid cell membranes indicated that the binding constant was 2 nM and each cell had an average of 1200 receptors. In addition to chemotactic receptors, one or more guanine nucleotide binding proteins are required for chemotaxis by RAW264 and the hybrid cells. This conclusion is based on the observation that chemotaxis of either RAW264 or hybrid cells is inhibited upon incubation of the cells with either cholera toxin or pertussis toxin. In all cases entry of the toxin is required and there is a correlation between toxin-catalyzed ADP-ribosylation of a guanine nucleotide binding protein and the inhibition of chemotaxis. Although both cholera toxin and pertussis toxin affect cAMP levels, elevated cAMP levels per se do not inhibit chemotaxis. By immunochemical and electrophoretic techniques, the pertussis toxin substrate involved in chemotaxis has been identified as $N_i$-2, a protein that is also found in brain.

**DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE**

## NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00943-06 LGCB

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Pathways of Methionine and Threonine Metabolism and Their Control in Higher Plants

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

| | | | |
|---|---|---|---|
| P.I. | J. Giovanelli | Research Chemist | LGCB NIMH |
| | S.H. Mudd | Chief, Section on Alkaloid Biosynthesis | LGCB NIMH |
| | A.H. Datko | Biologist | LGCB NIMH |

COOPERATING UNITS (if any)

None

LAB/BRANCH

Laboratory of General and Comparative Biochemistry

SECTION

Section on Alkaloid Biosynthesis

INSTITUTE AND LOCATION

NIMH, ADAMHA, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1.2 | 1.2 | 0 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects  ☐ (b) Human tissues  ☒ (c) Neither

  ☐ (a1) Minors

  ☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

At least 80% of the total activity of aspartokinase in crude extracts of Lemna paucicostata was inhibited by lysine, with the remaining activity inhibited by threonine. Inhibition by lysine was synergistically increased by S-adenosylmethionine, which by itself had no effect. Inhibition by lysine and threonine was additive, not cooperative. Aspartokinase activity extracted from Lemna was an order of magnitude greater than that reported by other workers for other plant tissues, and in large excess (approximately 20-fold) of the in vivo requirements for synthesis of the aspartate family of amino acids. Either lysine-sensitive or threonine-sensitive aspartokinase activities alone can support the combined in vivo flux into the aspartate family of amino acids. Severe inhibition of both forms of enzyme activity was required to reduce this flux below the normal requirement. No evidence was obtained for repression/derepression of aspartokinase in plants grown with amino acids of the aspartate family. A major conclusion from these combined data is that, contrary to suggestions of other workers, the step catalyzed by aspartokinase does not appear to be the overall rate-limiting one for entry of 4-carbon units into the aspartate pathway. Further, the findings confirm the absence of major "channeling" of lysine-sensitive or threonine-sensitive aspartokinases into separate biosynthetic branches of the aspartate family. The findings also help explain why little, if any, feedback regulation of threonine synthesis occurs in plants supplemented with threonine alone, while complete feedback regulation of threonine synthesis occurs in plants supplemented with both threonine and lysine.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02321-02 LGCB

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less Title must fit on one line between the borders )*

DNA Methylation and Gene E

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator ) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| P.I. | G. L. Cantoni | Chief, Laboratory of General and Comparative Biochemistry | LGCB |
| | R. Razin | Visiting Scientist, The Hebrew University Jerusalem, Israel | |
| Others: | S. Agostini | Guest Researcher | LGCB |
| | T. Gomi | Visiting Fellow | LGCB |

COOPERATING UNITS *(if any)*

Department of Cellular Biochemistry, The Hebrew University, Hadassah Medical School, Jerusalem, Israel; Department of Human Biopathology, University of Rome, La Sapienza, Rome, Italy

AB/BRANCH

Laboratory of General and Comparative Biochemistry

ECTION

Section on Proteins

NSTITUTE AND LOCATION

NIMH, ADAMHA, Bethesda, Maryland 20892

| OTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 3.5 | 3 | 0.5 |

HECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

UMMARY OF WORK *(Use standard unreduced type Do not exceed the space provided )*

When Friend Erythroleukemia cells (FELC) are exposed to a variety of chemical agents capable of inducing terminal differentiation their DNA undergoes a genome-wide demethylation in the absence of DNA replication. Considerable evidence has accumulated to indicate that demethylation of specific genes, or of portion of specific regions of the DNA, is correlated with gene expression. The transient genome-wide demethylation observed during FELC differentiation must be an expression of the fact that the overall pattern of DNA methylation changes during differentiation with some genes becoming active in transcription and others becoming silent. The mechanism of DNA demethylation is completely unknown: theoretically, inhibition during at least two cycles of DNA replication of maintenance methylase, an enzyme capable of methylating hemimethylated DNA, could result in DNA demethylation and changes in the DNA methylation pattern. However the inhibition of maintenance methylase can not be involved in the genome wide, transient demethylation that is observed in the early phases of FELC differentiation, since this occurs in the absence of DNA duplication.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

ZO1 MH 01037-19 LMB

PERIOD COVERED
October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
The Role of the Cell Membrane in Cellular Organization: A Molecular Study

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | D. M. Neville, Jr. | Chief, Sec. on Biophy. Chem. | LMB, NIMH |
| Others: | T. H. Hudson | Staff Fellow | LMB, NIMH |
| | J. W. Marsh | Staff Fellow | LMB, NIMH |
| | K. Srinivasachar | Visiting Associate | LMB, NIMH |
| | K.-H. Jung | Visiting Fellow | LMB, NIMH |

COOPERATING UNITS *(if any)*

LAB/BRANCH
Laboratory of Molecular Biology

SECTION
Section on Biophysical Chemistry

INSTITUTE AND LOCATION
NIMH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 5.3 | 3.3 | 2.0 |

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The general aim of this project is to determine the chemical interactions and energetics such as membrane potential and pH and ion gradients which are involved in the insertion of proteins into cellular membranes and/or the translocation of proteins across cellular membranes. The events are studied from the initial receptor binding to the final physiologic response or pathological response in the case of toxins such as ricin, colicins, diphtheria and tetanus toxins. Utilizing basic data from such studies immunotoxins (toxins linked to monoclonal antibodies) are constructed to serve as a new class of pharmacologic reagents to eliminate unwanted cell types such as cancer cells or T-4 lymphocytes in AIDS infections, or to manipulate specific cells such as T cell subsets to correct imbalences which exist in autoimmune diseases which can affect the CNS such as multiple sclerosis and lupus and cause psychosis. In addition immunotoxins continue to prove useful in deminishing the incidence of graft-versus-host-disease following bone marrow transplantation and thus will also have utility in enzyme replacement therapy and organ transplantation.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

ZO1 MH 01035-19 LMB

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

The Process of Lysogeny

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | H. A. Nash | Chief, Sec. on Molecular Genetics | LMB, NIMH |
| Others: | P. Kitts | Visiting Associate | LMB, NIMH |
| | M. Bruist | Research Associate | LMB, NIMH |
| | C.-C. Yang | Visiting Fellow | LMB, NIMH |

COOPERATING UNITS *(if any)*

Laboratory of Molecular Genetics, NICHD; Department of Microbiology, University of Illinois, Urbana, IL; and Cell Genetics Department, South San Francisco, CA

LAB/BRANCH

Laboratory of Molecular Biology

SECTION

Section on Molecular Genetics

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 4.75 | 3.75 | 1.0 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects
  ☐ (a1) Minors
  ☐ (a2) Interviews
☐ (b) Human tissues
☒ (c) Neither

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

We have investigated the mechanism by which the DNA of bacteriophage lambda integrates into the chromosome of its Escherichia coli host. We studied the role of DNA homology between the recombining sequences and ruled out two plausible alternatives for this requirement. We also determined that the two recombination partners interact with recombination proteins very differently. The bacterial partner obtains its recombinase only by collision with a nucleoprotein assembly formed on the viral partner. The genes for a second recombination protein have been placed on an overexpression vector and thus enabled the synthesis of large quantities of active protein.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

ZO1 MH 02228-03 LMB

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Genetic Neurobiology of Drosophila

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | H. A. Nash | Chief, Sec. on Molecular Genetics | LMB, NIMH |
| Others: | K. Weber | Graduate Student | Harvard Univ. |

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Molecular Biology

SECTION

Section on Molecular Genetics

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1.25 | 0.25 | 1.0 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

We have isolated mutants of the fruit fly Drosophila melanogaster that show an altered response to general anesthetics. We have mutangenized flies with ethylmethane sulfonate and found amongst their offspring mutants that are hypersensitive or resistant to halothane. These mutants form the starting point for a genetic and a molecular biological study of the mechanism by which anesthetics interfere with pain and consciousness.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
ZO1 MH 00934-15 LMB

PERIOD COVERED
October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
The Biochemical Basis of Peptide Receptor Activity

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

| | | | |
|---|---|---|---|
| PI: | W. A. Klee | Chief, Sec. on Regulatory Proteins | LMB, NIMH |
| Others: | D. L. Newton | Staff Fellow | LMB, NIMH |
| | J.-Y. Ye | Visiting Associate | LMB, NIMH |
| | R. C. Rice | Research Chemist | LC, NIADDK |
| | A. E. Jacobson | Research Chemist | LC, NIADDK |
| | M. Nirenberg | Chief, Lab. Biochem. Genetics | LBG, NIHLB |
| | P. Hargrave | Professor of Opthamology | University of Florida |

COOPERATING UNITS (if any)
Laboratory of Neurophysiology, NINCDS; Laboratory of Chemistry, NIADDK; and Laboratory of Biochemical Genetics, NIHLB

LAB/BRANCH
Laboratory of Molecular Biology

SECTION
Section on Regulatory Proteins

INSTITUTE AND LOCATION
NIMH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 4.0 | 3.0 | 1.0 |

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

In the past year we have continued our studies on reconstituted opiate receptors in purified systems. Purified G-proteins and adenylate cyclase were reconstituted into liposomes from detergent solutions by dialysis in the presence of phospholipids. In the reconstituted vesicles adenylate cyclase activity is stimulated by Gs and the stimulated activity is inhibited by Gi or by the beta-gamma subunit complex of bovine transducin. Further progress has been made in our efforts to obtain useful amounts of purified opiate receptors, and in characterizing the physical and biochemical properties of G-proteins.

We have identified a monoclonal antibody, directed against a defined region of the amino acid sequence of bovine transducin, which also recognizes opiate receptors from NG108-15 neuroblastoma x glimoa hybrid cells. A peptide corresponding to the epitope of the antibody inhibits precipitation of opiate receptors by the antibody. A peptide from the homologous region of the porcine brain muscarinic receptor not only blocks the antibody, but also activates a number of G-proteins both in membranes and in solutions of the purified proteins. We have thus identified the signal transmitting domain of G-protein coupled receptors.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01031-19 LNC

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

The Conversion of Phenylalanine to Tyrosine

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI | Seymour Kaufman | Chief | LNC NIMH |
| | Michael Davis | Senior Staff Fellow | LNC NIMH |
| | Jennifer Tipper | Senior Staff Fellow | LNC NIMH |
| | Yohsuke Minatogawa | Visiting Scientist | LNC NIMH |
| | Hans-Ulrich Siegmund | Visiting Fellow | LNC NIMH |

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Neurochemistry

SECTION

INSTITUTE AND LOCATION

ADAMHA, NIMH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 5.2 | 4.2 | 1.0 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Phenylalanine hydroxylase activity, measured at neutral pH, can be markedly increased by a brief exposure of the enzyme to alkaline pH.

Phenylalanine given to rats leads to an enhanced phosphorylation and activation of hepatic phenylalanine hydroxylase.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01032-19 LNC

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Biosynthesis of Catecholamines

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI | Seymour Kaufman | Chief | LNC NIMH |
| | Thomas Nelson | Staff Fellow | LNC NIMH |
| | Dominique Pigeon | Visiting Fellow | LNC NIMH |

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Neurochemistry

SECTION

INSTITUTE AND LOCATION

ADAMHA, NIMH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 2.2 | 1.2 | 1.0 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

A new rapid isolation procedure has been developed for the purification of tyrosine hydroxylase from brain and adrenal tissue.

A phosphatase that catalyzes the dephosphorylation-deactivation of tyrosine hydroxylase has been partially purified from rat brain. Its activity is affected by the pterin coenzyme for tyrosine hydroxylase.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01038-19 LNC

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Phenylketonuria and Other Diseases Caused by Defects in Biopterin-Dependent Enzymes

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

| | | | |
|---|---|---|---|
| PI | Seymour Kaufman | Chief | LNC NIMH |
| | Sheldon Milstien | Research Chemist | LNC NIMH |
| | Stanley Rapoport | Chief | LN NIA |

COOPERATING UNITS (if any)

Lab. of Neurosciences, National Institute on Aging

LAB/BRANCH

Laboratory of Neurochemistry

SECTION

INSTITUTE AND LOCATION

| | | |
|---|---|---|
| TOTAL MAN-YEARS:<br>0.7 | PROFESSIONAL:<br>0.7 | OTHER: |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

A determination of neopterin and biopterin levels in amniotic fluid has been used in the prenatal diagnosis of a possible case of a defect in tetrahydrobiopterin synthesis.

Alzheimer patients have low CSF levels of tetrahydrobiopterin.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01039-19 LNC

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Pteridine Biosynthesis

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | | |
|---|---|---|---|---|
| PI | Sheldon Milstien | Research Chemist | LNC | NIMH |
| | Seymour Kaufman | Chief | LNC | NIMH |

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Neurochemistry

SECTION

INSTITUTE AND LOCATION

ADAMHA, NIMH, Bethesda, Maryland 20892

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 0.7 | 0.7 | |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

A scheme has been developed to isolate and characterize all of the enzymes of tetrahydrobiopterin ($BH_4$) biosynthesis from rat brain. The wide distribution of tetrahydrobiopterin and these enzymes in the brain as well as the lack of effect of specific neurotoxins on some of the enzymes in the pathway suggests that tetrahydrobiopterin and/or these biosynthetic enzymes may have other roles than previously thought. Work is now under way to prepare antibodies to each of these enzymes to use for molecular cloning to obtain DNA probes to investigate the physiological roles.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02262-03 NPB

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Electroretinography in Schizophrenia

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

Myles Jay Jaffe, O.D. Ph.D., Senior Staff Fellow, Neuropsychiatry Branch, IRP, NIMH

Dr. Craig N. Karson, Staff Psychiatrist, Clinical Brain Disorders Branch, IRP, NIMH

COOPERATING UNITS (if any)

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1.0 | 1.0 | 0 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The ganzfeld electroretinogram has revealed that patients with chronic Parkinson's disease have a diminished sensitivity of their retina to light; this defect can, in part, be restored by an i.v. infusion of L-dopa. Together, these findings indicate that the retina is another CNS structure that is involved in Parkinson's disease. In addition, morphine modulates the sensitivity of the retina to light. In combination with other studies, we have found that the actions of morphine may be related to the action of dopamine within the retina.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02263-03 NPB

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Haloperidol Pharmacodynamics and Clinical Response in Schizophrenia

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

Darrell G. Kirch, M.D., Senior Staff Fellow, Neuropsychiatry Branch, IRP, NIMH

Dr. Llewellyn B. Bigelow, Associate Clinical Director for the William A. White Division, Saint Elizabeths Hospital; Dr. Gregory M. Straw, Medical Staff Fellow, NPB, IRP, NIMH; Dr. Markku Linnoila, NIAAA; Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH; Dr. Greg Gerhardt, University of Colorado Health Sciences Center; Dr. Robert Freedman, University of Colorado Health Sciences Center

COOPERATING UNITS (if any)

NIAAA; University of Colorado Health Sciences Center

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Clinical Neuropsychiatry

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1.0 | 0.5 | 0.5 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

As part of a standardized research sequence in the NIMH intramural clinical program located at Saint Elizabeths, patients with schizophrenia are withdrawn from neuroleptic medication and then (after clinical relapse) treated with a fixed dose of haloperidol. This has in turn allowed initiation of a variety of studies regarding the pharmacokinetics of haloperidol. Other pharmacological issues examined in these patients are drug-drug interactions (specifically involving haloperidol and a number of other drugs, including nicotine, caffeine, retinoic acids, and dopaminergic agonists). In addition, basic science investigations regarding these drugs are being conducted.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

**NOTICE OF INTRAMURAL RESEARCH PROJECT**

PROJECT NUMBER

Z01 MH 02264-03 NPB

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Post Mortem Brain Tissue Examination in Psychiatric Disorders

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Joel E. Kleinman, M.D., Ph.D., Chief, Section on Clinical Brain Studies, NPB, IRP, NIMH

Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH; Dr. Craig N.Karson Staff Psychiatrist, NPB, IRP, NIMH; Dr. Esa Korpi, State Alcohol Monopoly, Helsinki Finland; Dr. Markku Linnoila, NIAAA, NIMH; Dr. Farouk Karoum, Chemist, NPB, IRP, NIMH; Dr. Daniel Weinberger, Chief, Section on Clinical Neuropsychiatry, NPB, IRP, NIMH; Dr. Anita Feenstra, Visiting Associate, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

State Alcohol Monopoly, Helsinki, Finland; NIAAA; Johns Hopkins University; Clinical Neuroscience Branch, NIMH

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Clinical Brain Studies

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1.5 | 1.0 | 0.5 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project has been transferred to the Clinical Brain Disorders Branch.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02267-03 NPB

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Brain Electrical Activity Mapping in Neuropsychiatric Patients

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Dr. Craig N. Karson, Staff Psychiatrist, NPB, IRP, NIMH

Dr. Terry Goldberg, Special Expert, NPB, IRP, NIMH; Dr. Karen F. Berman, Staff Psychiatrist, NPB, IRP, NIMH; Dr. Ralph Fawcett, Medical Staff Fellow, NPB, IRP, NIMH; Dr. Richard Coppola, Sr. Engineer Officer, NPB, IRP, NIMH; Dr. Daniel R. Weinberger, Chief, Section on Clinical Neuropsychiatry, NPB, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Clinical Neuropsychiatry

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

| | | |
|---|---|---|
| TOTAL MAN-YEARS:<br>1.0 | PROFESSIONAL:<br>0.5 | OTHER:<br>0.5 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project has been transferred to the Clinical Brain Disorders Branch.

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 MH 02268-03 NPB

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

The Clinical Phenomenology of Multiple Personality Disorder

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Frank W. Putnam, M.D., Staff Psychiatrist, Neuropsychiatry Branch, IRP, NIMH

Dr. E.A. Silberman, USUHS; Dr. Robert Post, Biological Psychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

USUHS
Biological Psychiatry Branch, IRP, NIMH

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 0.33 | 0.17 | 0.17 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project was transferred to the Laboratory of Developmental Psychology in June 1986.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02269-03 NPB

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

The Development, Reliability and Validity of a Dissociation Scale

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Frank W. Putnam, M.D., Staff Psychiatrist, Neuropsychiatry Branch, IRP, NIMH

Dr. Eve Bernstein, Department of Psychology, American University

COOPERATING UNITS *(if any)*

Department of Psychology, American University

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

| | | |
|---|---|---|
| TOTAL MAN-YEARS:<br>0.33 | PROFESSIONAL:<br>0.17 | OTHER:<br>0.17 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
 ☐ (a1) Minors
 ☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project was transferred to the Laboratory of Developmental Psychology in June 1986.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02270-03 NPB

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

The Psychophysiology of Multiple Personality

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Frank W. Putnam, M.D., Staff Psychiatrist, Neuropsychiatry Branch, IRP, NIMH

Dr. Karen F. Berman, Staff Psychiatrist, NPB, IRP, NIMH; Dr. Daniel Weinberger, Chief, Clinical Neuropsychiatry Section, NPB, IRP, NIMH; Dr. Richard Coppola, Engineer, Clinical Neuropsychiatry Section, NPB, IRP, NIMH; Dr. Robert M. Post, Biological Psychiatry Branch, IRP, NIMH; Dr. Theodore Zahn, Laboratory of Psychology and Psychopathology, BPB, NIMH

COOPERATING UNITS *(if any)*

Biological Psychiatry Branch, IRP, NIMH

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

| | | |
|---|---|---|
| TOTAL MAN-YEARS:<br>0.33 | PROFESSIONAL:<br>0.17 | OTHER:<br>0.17 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project was transferred to the Laboratory of Developmental Psychology in June 1986.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02273-03 NPB

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

White House Cases: Predictors of Future Violence

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

David Shore, M.D., Staff Psychiatrist, NPB, IRP, NIMH

C. Richard Filson, Ed.D., Richardson Division, SEH; Kenneth Baker, Behavioral Research Section, U.S. Secret Service; Dr. Charles Kinderman, Bureau of Justice Statistics, U.S. Department of Justice; Ken Candell, Uniform Crime Reporting Division; William Garvie, Identification Division, FBI

COOPERATING UNITS *(if any)*

Richardson Div., St. Elizabeths Hosp., Wash. D.C.; Behavioral Research Sect., Intelligence Div., U.S. Secret Service; Bureau of Justice Statistics, U.S. Department of Justice; Uniform Crime Reporting Div. and Identification Div., FBI

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Aging

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1.0 | 1.0 | 0 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project has been completed and terminated.

PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 MH 02274-03 NPB

PERIOD COVERED
October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Exploration of New Methods for Treatment of Intractable Epilepsy

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*
Janice Stevens, M.D., Medical Officer, Neuropsychiatry Branch, IRP, NIMH

Dr. William J. Freed, Chief, Preclinical Neurosciences Section, NPB, IRP, NIMH
NINCDS, Bethesda, Maryland

COOPERATING UNITS *(if any)*

LAB/BRANCH
Neuropsychiatry Branch

SECTION
Section on Aging

INSTITUTE AND LOCATION
NIMH, Saint Elizabeths Hospital, Washington, D.C.

| | | |
|---|---|---|
| TOTAL MAN-YEARS: 1.25 | PROFESSIONAL: 1.0 | OTHER: 0.25 |

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

In an attempt to devise more effective methods for treatment of epilepsy that is intractable by conventional modern medical therapy or surgical intervention, we explored the feasibility of brain grafts of GABAergic brain tissue to specific brain areas in rat models of epilepsy. We worked with two satisfactory experimental epilepsy models in the laboratory: (1) audiogenic seizures in genetically predisposed rats and (2) amygdala kindled rats.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02275-03 NPB

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Search for Virus in CSF and Postmortem Brain of Patients with Schizophrenia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Janice R. Stevens, M.D., Medical Officer, Neuropsychiatry Branch, IRP, NIMH

Dr. David Asher, NINCDS, Bethesda, Maryland; Dr. Joan Schwartz, NINCDS, Bethesda, Maryland; Dr. Peggy Swoveland, Dept. of Neurology, Univ. of Maryland; Dr. David Jacobowitz, NIMH, Bethesda, Maryland

COOPERATING UNITS *(if any)*

NINCDS
University of Maryland
NIMH

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Aging

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1.25 | 1.0 | 0.25 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Based on evidence that an infectious agent or agents may play a role in the etiology of some schizophrenic illnesses, we are culturing fresh CSF from patients with schizophrenia and from control subjects on human neuroblastoma cells. Our previous studies have included immunocytochemical investigations for antigens to cytomegalovirus (CMV), herpes simplex virus (HSV), varicella virus, rubella and mumps. Although sporadic cases have shown positive results with immunocytochemical studies, these have been inconsistent and rare. We have also undertaken in situ hybridization probes for CMV, and cultivation of schizophrenic and control brain specimens on cultures of human and non-human neural tissue without success. Using special stains for glia we have evaluated the brains of guinea pigs and primates previously inoculated with schizophrenic and control brain tissue. During the past year we have investigated the effects of cerebrospinal fluid and sterile brain tissue from schizophrenic patients on the growth, peptide production and morphology of cultured human neuroblastoma cells. One line of human neuroblastoma cells (SHEP) has shown a consistent change in growth with loss of contact inhibition and piling up of cells to higher confluence commencing several months after incubation with schizophrenic CSF in 6 out of 7 cases, but in no control inoculated cells. Adenylcyclase production is increased in schizophrenic CSF treated cells and the effect on cell growth has been passaged with cell free media. Two dimensional electrophoresis gels demonstrate differences in protein in schizophrenic compared with control gels. Further studies in progress with these transformed cells include electron microscopic examination (Dr. Peggy Swoveland), studies for reverse transcriptase (negative), ELISA and immunocytochemical studies following application of control and schizophrenic sera to search for antibodies (negative so far).

PHS 6040 (Rev. 1/84) GPO 914-918

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| DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE<br>**NOTICE OF INTRAMURAL RESEARCH PROJECT** | PROJECT NUMBER<br>Z01 MH 02277-03 NPB |

PERIOD COVERED
October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Regional Cerebral Blood Flow in Neuropsychiatric Patients and in Normal Subjects

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*
Daniel Weinberger, M.D., Chief, Section on Clinical Neuropsychiatry, NPB, NIMH;
Karen Faith Berman, M.D., Staff Psychiatrist, NPB, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH
Neuropsychiatry Branch

SECTION
Section on Clinical Neuropsychiatry

INSTITUTE AND LOCATION
NIMH, Saint Elizabeths Hospital, Washington, D.C.

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1.0 | 0.5 | 0.5 |

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project has been transferred to the Clinical Brain Disorders Branch.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 MH 01040-19 LNC

PERIOD COVERED
October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Molecular Biology of the Pterin-Dependent Hydroxylases and Ancillary Enzymes

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI | Seymour Kaufman | Chief | LNC NIMH |
| | Sheldon Milstien | Research Chemist | LNC NIMH |
| | Bruce Citron | Senior Staff Fellow | LNC NIMH |
| | Y. C. Liu | Visiting Fellow | LNC NIMH |
| | John Donlon | Visiting Scientist | LNC NIMH |

COOPERATING UNITS *(if any)*

LAB/BRANCH
Laboratory of Neurochemistry

SECTION

INSTITUTE AND LOCATION
ADAMHA, NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS: 2.2
PROFESSIONAL: 2.2
OTHER:

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

A sufficiently extensive cDNA clone of rat liver phenylalanine hydroxylase has been isolated and sequenced.

A composite DNA molecule containing this cDNA and the E. coli lac promoter, operator, and translation initiation site has been constructed and placed in a host that is inducible for this operon.

Elevated phenylalanine hydroxylase mRNA levels have been observed in diabetic rats.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00981-21 LNP

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Mechanical, Thermal and Optical Signs of Excitation in the Nervous System

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | Ichiji Tasaki | Chief, Unit of Neurobiology | LNP, NIMH |
| Others: | Nobuko Tasaki | Guest Worker | LNP, NIMH |

COOPERATING UNITS *(if any)*

LAB/BRANCH

Unit on Neurobiology, Laboratory of Neurophysiology

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS: PROFESSIONAL: OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Due to the transfer of principal investigator to the Laboratory of Cell Biology, this project has been assigned number Z01 MH 02396-01 LCB.

|  |  |
|---|---|
| **DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE**<br>**NOTICE OF INTRAMURAL RESEARCH PROJECT** | PROJECT NUMBER<br>Z01 MH 01092-09 LNP |

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

The Frontal Lobe and the Cerebral Control of Behavior

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

|  |  |  |  |
|---|---|---|---|
| PI: | Steven P. Wise | Research Biologist | LNP, NIMH |
| Others: | Kiyoshi Kurata | Visiting Fellow | LNP, NIMH |
|  | Eilon Vaadia | Visiting Associate | LNP, NIMH |
|  | Shraga Hocherman | Visiting Associate | LNP, NIMH |

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Neurophysiology

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH Animal Center, Poolesville, Maryland 20837

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 2.4 | 2.4 |  |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The primate frontal lobe consists of three main parts: the primary motor cortex (MI), the prefrontal cortex, and the nonprimary motor cortex. Previous work on this project has shown that the nonprimary motor cortex can be divided into at least two fields: the supplementary motor cortex (SM) and the premotor cortex (PM). Definition of these cortical fields depended on an analysis of neuronal responses to peripheral inputs, thresholds for evoking movements with intracortical electrical stimulation, the properties of single neurons during the performance of several visuomotor tasks, and cytoarchitectonics. After defining the areas, we directed our studies, using the techniques of behavioral neurophysiology developed in this laboratory, toward the nonprimary motor cortex. Our results support the hypothesis that PM and SM contribute to sensorially-referenced behaviors especially those guided by abstract or arbitrary sensory cues. These studies have provided new insight into the processes by which animals, including humans, prepare for action in relation to partially predictable environmental events. The preparation for receipt of informa(attention) and for future action (motor set) represent higher brain functions amenable to both quantitative and qualitative neurophysiological analysis and appear to be a property conferred by the frontal cortex.

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| DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE<br>NOTICE OF INTRAMURAL RESEARCH PROJECT | PROJECT NUMBER<br>Z01 MH 01096-03 LNP |

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Spatial Organization of the Primate Motor Cortex

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

|  |  |  |  |
|---|---|---|---|
| PI: | Andrew R. Mitz | Senior Staff Fellow | LNP, NIMH |
| Others: | Steven P. Wise | Research Biologist | LNP, NIMH |
|  | Moshe Godschalk | Visiting Associate | LNP, NIMH |

COOPERATING UNITS (if any)

LAB/BRANCH

Laboratory of Neurophysiology

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH Animal Center, Poolesville, Maryland 20837

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1.9 | 1.9 |  |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The purpose of this project is to examine the internal organizations and the interrelationship among motor areas of the frontal lobe, including the primary motor cortex (MI), the supplementary motor cortex (SM), the frontal eye fields (FEF) and the premotor cortex (PM). The model species chosen for study is the rhesus monkey, because these motor areas have been best characterized in this species. In the first part of this project intracortical microstimulation is being employed to examine the efferent topography of the motor areas.

In the second part of the project single-unit recording will be employed to examine the possible involvement of the premotor cortex in learning new stimulus-response relationships. It is the goal of this part of the project to determine the roles played by each cortical motor area in recall and execution of learned motor behaviors.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

## NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01097-01 LNP

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Activity of Corticostriatal Neurons in Motor Cortex of Primates During Wrist Movement

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

| | | | |
|---|---|---|---|
| PI: | Melvyn P. Heyes | Visiting Associate | LNP, NIMH |
| Others: | Steven P. Wise | Research Biologist | LNP, NIMH |

COOPERATING UNITS (if any)

LAB/BRANCH

Laboratory of Neurophysiology

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH Animal Center, Poolesville, Maryland 20837

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 0.4 | 0.4 | |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
 ☐ (a1) Minors
 ☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Although it is well known that the major input to the striatum originates in the cerebral cortex, virtually nothing is known about the type of information conveyed by the corticostriatal pathway. The part of the striatum that receives input from the primary motor cortex is the putamen. Putamen neurons discharge at or after the onset of EMG activity and reflect the direction of movement per se, whereas many neurons in the primary motor cortex discharge prior to the onset of EMG activity and reflect individual muscle activity independent of the direction of movement. To investigate corticostriatal (CS) activity during movement, we developed a strategy to identify CS neurons and quantitate their activity, their timing with respect to movement, and their relationship to the pattern of muscle activation in rhesus monkeys. Our observations indicate that motor information is conveyed via the CS pathway and that CS neurons more closely resemble primary motor cortex neurons than putamen neurons with respect to their timing and relationship to the patterns of muscle activity. It is possible, therefore, that motor disorders could result from excess in CS activity that causes abnormal contraction of muscles and limb position in space.

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|---|---|
| DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE<br>**NOTICE OF INTRAMURAL RESEARCH PROJECT** | PROJECT NUMBER<br>Z01 MH 01098-01 LNP |

PERIOD COVERED

February 1, 1987 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Anatomical Analysis of Neuronal Circuits

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: Chisato Asanuma Stanfield Staff Fellow LNP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Neurophysiology

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH Animal Center, Poolesville, Maryland 20837

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 0.67 | 0.67 | |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
 ☐ (a1) Minors
 ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Previous studies of the dendritic structure of neurons have predominantly relied on the century-old Golgi methods and the technique of injecting biological markers into single neurons in vivo. For technical reasons, however, it has been difficult to effectively combine these methods with other neuroanatomical labeling techniques. The recently introduced method of intracellularly injecting a fluorescent dye, Lucifer yellow, in fixed tissue slices is capable of providing a complete picture of neuronal geometry and has the potential for use in conjunction with other neuroanatomical techniques. This project involves intracellular injection of Lucifer yellow in combination with retrograde labeling techniques and immunohistochemistry, and its objective is to extend the analysis of neuronal connectivity and transmitter specificities to a finer level than previously possible. Initially two questions will be addressed: (1) is there a point-to-point reciprosity between thalamocortical axon collaterals that innervate the thalamic reticular nucleus and the neurons in that nucleus which project back to the thalamus; and (2) where on the dendrites of reticular nucleus neurons do thalamocortical axon collaterals terminate?

| DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE<br>**NOTICE OF INTRAMURAL RESEARCH PROJECT** | PROJECT NUMBER<br>Z01 MH 01099-01 LNP |
|---|---|

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Neurochemical Interactions Between Cortical and Striatal Dopaminergic Activity

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | | |
|---|---|---|---|
| PI: | Melvyn P. Heyes | Visiting Associate | LNP, NIMH |
| Others: | Ikuro Namura | Visiting Fellow | LCS, NIMH |
| | Stephen Suomi | Chief | LCE, NICHD |

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Neurophysiology

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH Animal Center, Poolesville, Maryland 20837

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 0.5 | 0.5 | |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Disturbances in the balance of regional brain dopaminergic activity have been implicated in the symptomatology of schizophrenia. Recent studies suggest that dysfunction of the dorsolateral prefrontal cortex (DLPFC) may cause the impaired motivation, shallow affect, and deficiencies in the performance of problem solving tasks suffered by schizophrenics. Similar deficits are produced in primates by dopamine depletion in the DLPFC. Together these observations suggest a role for DLPFC dopaminergic neurons in cognitive functions subserved by this area. In one series of experiments in rats, dopamine depletion in the medial frontal cortex (MFC), a possible rodent homologue of the DLPFC of primates, resulted in increased dopaminergic activity in striatum. Our observations in rats showed that dopamine depletion in the MFC by local injection of $MPP^+$ or 6-OHDA was associated with increased dopaminergic in nucleus accumbens, but not the caudatoputamen. This project will now be extended to primates to further test the hypothesis that corticostriatal abnormalities underlie psychotic disorders in a species more closely related and similar to humans.

| DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE<br>**NOTICE OF INTRAMURAL RESEARCH PROJECT** | PROJECT NUMBER<br>Z01 MH 02244-03 NPB |
|---|---|

PERIOD COVERED
October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Behavioral Effects of Neurotoxic Substances and Their Neurochemical Correlates

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*
Jean Lud Cadet, M.D., Medical Staff Fellow, Section on Clinical Neuropsychiatry, NPB, IRP, NIMH

Dr. William J. Freed, Chief, Preclinical Neurosciences Section, NPB, IRP, NIMH; Dr. Richard Rothman, Guest Worker, Laboratory of Preclinical Pharmacology, IRP, NIMH; Dr. De-Maw Chuang, Laboratory of Preclinical Pharmacology, IRP, NIMH; Dr. Michael Iadarola, Staff Fellow, National Institute of Dental Research; Dr. Anthony Adinolfi, University of California, Los Angeles, California

COOPERATING UNITS *(if any)*
National Institute of Dental Research (NIDR); University of California, Los Angeles, California

LAB/BRANCH
Neuropsychiatry Branch

SECTION
Section on Clinical Neuropsychiatry

INSTITUTE AND LOCATION
NIMH, Saint Elizabeths Hospital, Washington, D.C.

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 0.5 | 0.5 | 0 |

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project has been terminated because the Principal Investigator left NIMH.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02245-03 NPB

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Functional Consequences of Experimental Nerve Lesions

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Luis de Medinaceli, M.D., Visiting Scientist, Neuropsychiatry Branch, IRP, NIMH

Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Aging

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

| | | |
|---|---|---|
| TOTAL MAN-YEARS:<br>1.0 | PROFESSIONAL:<br>0.33 | OTHER:<br>0.67 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Crush lesions were made on sciatic nerves of rats. We examined the influence on recovery of the time elapsed between successive injuries and of location and number of damaged sites. The results were assessed over a post-operative period of 2.5 months by studying tracks obtained from walking rats. This study demonstrated the central role of basal lamina tube lesions in nerve injuries. In contrast, neither injury to the tissue of the nerve (Schwann cells), nor to the neurite itself influenced the functional outcome.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02246-03 NPB

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Post-Traumatic Autoimmune Reaction In Peripheral Nerve

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Luis de Medinaceli, M.D., Visiting Scientist, Neuropsychiatry Branch, IRP, NIMH

Dr. Yen-Nung Wang, Visiting Associate, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Aging

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1.0 | 0.33 | 0.67 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This study was conducted to show whether local autoimmune reactions can be observed after injury to the sciatic nerve in the rat. Furthermore, we attempted to correlate the intensity of the immunological reaction with the severity of nerve damage, the type of surgical treatment and the degree of functional recovery. A direct influence of autoimmunization was found. Its effect on functional recovery was moderate but constant.

PHS 6040 (Rev 1/84)

GPO 914-918

|  |  |
|---|---|
| DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE<br>**NOTICE OF INTRAMURAL RESEARCH PROJECT** | PROJECT NUMBER<br>Z01 MH 02247-03 NPB |

PERIOD COVERED
October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Prediction of Outcome of Peripheral Nerve Injuries - A Probability Model

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*
Luis de Medinaceli, M.D., Visiting Scientist, Neuropsychiatry Branch, IRP, NIMH

Dr. Robert R. Rawlings, Mathematical Statistician, Division of Biometry and Epidemiology, NIAAA; Dr. Yen-Nung Wang, Visiting Associate, Neuropsychiatry Branch, IRP, NIMH; Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*
Division of Biometry and Epidemiology, NIAAA

LAB/BRANCH
Neuropsychiatry Branch

SECTION
Section on Aging

INSTITUTE AND LOCATION
NIMH, Saint Elizabeths Hospital, Washington, D.C.

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1.0 | 0.33 | 0.67 |

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The long term functional consequences of peripheral nerve injuries are notoriously unpredictable. We hypothesized that considering the individual regrowth of the elementary components of a nerve (the neurites) rather than the global regeneration of the organ could lead to a better understanding of the mechanisms of nerve repair.

We postulated that the regrowth of any individual neurite can be defined in terms of its influence on recovery, the three main possibilities being valid, neutral and invalid regrowth. We have designed a probability model describing the prospects of regrowth for nerve composed of several types of fibers. This model is being tested in pre-determined situations to judge its validity. We found that possible variations in the outcome of nerve injuries could be explained by a parsimonious hypothesis: the randomness of regrowth.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02250-03 NPB

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Purification of Messenger RNAs Encoding for Neurotrophic Factors in the Rat Brain

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Anne-Marie Duchemin, M.D., Visiting Fellow, Neuropsychiatry Branch, IRP, NIMH

Dr. Thanh Tam Quach, Visiting Associate, Neuropsychiatry Branch, IRP, NIMH; Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH; Dr. Bruce K. Schrier, Laboratory of Developmental Neurobiology, NICHD, NIH

COOPERATING UNITS *(if any)*

Laboratory of Developmental Neurobiology, NICHD, NIH

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 0.33 | 0.33 | 0 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Neurotrophic factors have been shown to appear in the rat brain after lesion. This project intends the molecular cloning of the gene encoding for these lesion-induced trophic factors in the brain. First, we developed the assays to produce these factors and test for their neurotrophic activity. A fraction of mRNA, prepared from lesioned rat brain, responsible for neurotrophic activity was found by in vivo translation into proteins in Xenopus Laevis oocytes. This fraction is now being used to construct a cDNA library in the vector pGEM blue. We also contructed a cDNA library specific for lesioned rat brain in the vector bluescribe M 13. By differential colony hybridization, we have selected positive clones and some of these have been tested for coding for neurotrophic activity.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

**NOTICE OF INTRAMURAL RESEARCH PROJECT**

PROJECT NUMBER

Z01 MH 02251-03 NPB

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Distribution of Brain Somatostatin mRNA

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Anita Feenstra, Ph.D., Visiting Associate, NPB, IRP, NIMH

Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1.0 | 0.5 | 1.0 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

We have initiated a study of the local distribution of somatostatin mRNA in brains of patients with schizophrenia and Huntington's disease. The mRNA extraction method was adopted for brain tissue. Brains of patients and normal brains are being collected, and the proper area's are dissected.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 MH 02252-03 NPB

PERIOD COVERED
October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Behavioral Pharmacology and Toxicology

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

William J. Freed, Ph.D., Chief, Preclinical Neurosciences Section, NPB, IRP, NIMH

Dr. Renaud de Beaurepaire, Visiting Associate, NPB, IRP, NIMH; Dr. Jack A. Grebb, Laboratory of Molecular and Cellular Neuroscience, Rockfeller University, New York; Dr. Richard Shelton, Department of Psychiatry, Vanderbilt University School of Medicine, Nashville, Tenn.; Dr. Saul Schwarcz, Department of Neurosurgery, Naval Medical Center, Bethesda, Maryland

COOPERATING UNITS *(if any)*
Vanderbilt University School of Medicine, Nashville, Tenn.
Department of Neurosurgery, Naval Medical Center, Bethesda, Maryland
Laboratory of Molecular and Cellular, Rockfeller University, New York

LAB/BRANCH
Neuropsychiatry Branch

SECTION
Preclinical Neurosciences Section

INSTITUTE AND LOCATION
NIMH, Saint Elizabeths Hospital, Washington, D.C.

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 3.0 | 0.5 | 2.5 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The project on behavioral pharmacology and toxicology is aimed at the elucidation of neuropharmacological processes involved in abnormal brain function and at the development of techniques to intervene in abnormal brain function through pharmacological manipulations. These studies involve the induction of abnormal behavioral and physiological states through administration of drugs and other maniputations, and attempts to alter behavior and physiological states by pharmacological manipulations. Particular topics of interest are areas known to be associated with the actions of neuroleptic drugs and drug-induced psychoses. These include (i) phencyclidine, which in humans can induce abnormalities resembling schizophrenia; (ii) calcitonin and calcium-channel inhibitors and activators, are under investigation because of the possible relationships between calcium mechanisms and long-term changes in neuronal function induced by chronic neuroleptics; (iii) seizures and other phenomena related to the quisqualate type of glutamate receptors are of particular interest because of the close association between glutamate synapses and dopamine synapses on striatal neurons; (iv) changes in various neuronal systems particularly excitatory amino acid systems induced by chronic neuroleptic administration are investigated in order to contribute to an understanding of the mechanisms of action of neuroleptics.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

**NOTICE OF INTRAMURAL RESEARCH PROJECT**

PROJECT NUMBER

Z01 MH 02253-03 NPB

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Brain Tissue Transplantation

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

William J. Freed, Ph.D., Chief, Preclinical Neurosciences Section, NPB, IRP, NIMH

Dr. Urmi Patel-Vaidya, Staff Fellow, NPB, IRP, NIMH; Renaud de Beaurepaire, Visiting Associate, NPB, IRP, NIMH; Dr. Herbert Geller, Rutgers University, New Brunswick, New Jersey; Dr. Jeff Laskin, Rutgers University, New Brunswick, New Jersey; Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH; Dr. Saul Schwarz, Department of Neurosurgery, Naval Hospital, Bethesda, Maryland; Dr. Ronald Hargraves, Department of Neurosurgery, Naval Hospital, Bethesda, Maryland

COOPERATING UNITS *(if any)*

Rutgers University, New Jersey; Naval Medical Center, Bethesda, Maryland; University of Minnesota; University of Michigan

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Preclinical Neurosciences Section

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 3.0 | 0.5 | 2.5 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

These studies are primarily aimed at transplantation of catecholamine-containing tissues, including adrenal medulla, tumor cells, and embryonic brain tissue into the brain. The purpose of these experiments is to elucidate the properties of these tissues after transplantation and the response of the host brain to the transplanted tissues. Specifically, these experiments employ non-primate animal models to (1) develop the techniques of brain tissue transplantation for clinical use in Parkinson's disease; (2) develop brain tissue transplantation techniques so that they eventually may be applicable to other disorders, such as schizophrenia or Alzheimer's disease if and when these disorders become well enough understood to permit such applications; and (3) elucidate factors that control the development of the brain and responses of the brain to injury or impairment, with particular emphasis on the nigrostriatal dopamine system. During the past reporting year, significant progress has been made in these areas.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02255-03 NPB

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Calcium Channel Inhibitors: Interactions Systems - Human Studies

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Gregory M. Straw, M.D., Medical Staff Fellow, Neuropsychiatry Branch, IRP, NIMH

Dr. Darrell Kirch, Senior Staff Fellow, NPB, IRP, NIMH; Dr. Llewellyn B. Bigelow, Associate Clinical Director for WAW Division, Saint Elizabeths Hospital; Dr. Edward Taylor, Clinical Social Worker, WAW Division, Saint Elizabeths Hospital, Dr. Richard Suddath, Medical Staff Fellow, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Preclinical Neurosciences Section

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 0.25 | 0.25 | 0 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Calcium channel inhibitors (CCI's) are thought to affect calcium flux through membrane bound channels as their major site of action. There are reports of clinical trials involving over 150 patients suggesting that CCI's also have beneficial effects in neuropsychiatric disorders. There are four major subclasses of CCI's; each appears to have unique combinations of biochemical and behavioral properties. Additional studies have suggested a complex interaction between dopamine receptor function and calcium channels. We have completed a study of the clinical effects of verapamil in a schizophrenic population where trends toward improvement did not reach statistical significance. We have proceeded with the protocol to examine the effects of nifedipine in a similar cohort. Results on the first eight completed subjects have shown two trends: 1) an increase in "negative" symptoms of schizophrenia while on active nifedipine, and 2) a decrease in abnormal involuntary movements on the AIMS (abnormal involuntary movement scale) while on active nifedipine. Also, a comparison of the placebo periods before and after active nifedipine suggests a significant sequence effect measured by continued worsening of the BPRS (brief psychiatric rating scale) scores after active nifedipine.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

**NOTICE OF INTRAMURAL RESEARCH PROJECT**

PROJECT NUMBER
Z01 MH 02256-03 NPB

PERIOD COVERED
October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Defect Symptoms in Schizophrenia: Their Measurement, Correlates, and Treatment

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*
Darrell G. Kirch, M.D., Senior Staff Fellow, NPB, IRP, NIMH

Dr. Andrei C. Jaeger, New York State Psychiatric Institute; Dr. Edward H. Taylor, Clinical Social Worker, WAW Division, Saint Elizabeths Hospital; Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

New York State Psychiatric Institute

LAB/BRANCH
Neuropsychiatry Branch

SECTION
Section on Clinical Neuropsychiatry

INSTITUTE AND LOCATION
NIMH, Saint Elizabeths Hospital, Washington, D.C.

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 2.0 | 1.0 | 1.0 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Renewed interest in the role of negative symptoms in "defect state" schizophrenia encouraged us to develop a "Negative Symptom Rating Scale (NSRS)" to more efficiently measure this syndrome. A study has been conducted performing a factor analysis of the NSRS. Studies are being conducted to explore the relationship between schizophrenia, social intelligence, general intelligence, negative symptoms and premorbid social functioning in schizophrenic patients.

PHS 6040 (Rev 1/84)

GPO 914-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

## NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02257-03 NPB

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Biochemical and Neuroradiologic Abnormalities in Tardive Dyskinesia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

James B. Lohr, M.D., Medical Staff Fellow, Neuropsychiatry Branch, NIMH

Dr. Jean L. Cadet, Medical Staff Fellow, NPB, IRP, NIMH; Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Aging

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1.0 | 0.5 | 0.5 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

We have been studying the efficacy of antioxidant therapy for tardive dyskinesia (TD). The treatment involves alpha-tocopherol. Results reveal a significant improvement in movement disorder and a trend toward improvement in psychopathology in schizophrenic and schizoaffective patients with TD after administration of alpha-tocopherol, but no change in neuroleptic-induced parkinsonism with this agent.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02258-03 NPB

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Quantitative Neuropathology of Aging and Neuropsychiatric Disorders

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

James B. Lohr, M.D., Medical Staff Fellow, NPB, IRP, NIMH

Dr. Dilip Jeste, Department of Psychiatry and Neurosciences, University of California at San Diego; Dr. Joseph Parisi, Chairman, Department of Neuropathology, Armed Forces Institute of Pathology, Bethesda, Maryland; Dr. Francine Benes, Department of Psychiatry, McLean Research Center, Boston, MA.

COOPERATING UNITS *(if any)*

Dept. Psychiat. Neurosci., Univ. of California at San Diego; Dept. Neurol., George Washington Univ. Hosp., Washington, D.C.; Dept. Neuropathol., Armed Forces Inst. Pathol., Bethesda, MD; Dept. Psychiatry, McLean Research Center, Boston, MA

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Aging

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1.0 | 0.5 | 0.5 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

We have been studying quantitative volume, neuronal density, neuronal size and nuclear size in selected areas of brains from patients with certain neuropsychiatric disorders as well as normal controls from different age groups. Results to date indicate that there is normally age-related Purkinje cell loss in the cerebellum, pyramidal cell loss in area CA4 of the hippocampus, and neuron loss in the locus ceruleus. In schizophrenic subjects, we found a significant decrease in the pyramidal cell density in area CA4 of the hippocampus, mainly in the left hemisphere when anteriorly compared to controls. We found no significant morphological differences between schizophrenic patients, affective disorder patients and normal controls in cerebellum. There was a trend toward a reduction in the volume of the locus ceruleus in schizophrenics, without a loss of neurons.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02259-03 NPB

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Peripheral and Central Catecholamine Turnover in Mental Illnesses

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Farouk Karoum, Ph.D., Chemist, Neuropsychiatry Branch, IRP, NIMH

Dr. Esa Korpi, Research Laboratories, Helsinki, Finland; Dr. Craig N. Karson, Staff Psychiatrist, NPB, IRP, NIMH; Dr. William B. Lawson, Faculty Member, University of California, Irvine, California; Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH; Dr. Markku Linnoila, LCS, DICBR, NIAAA; Dr. Alan J. Zametkin, Laboratory of Clinical Science, IRP, NIMH

COOPERATING UNITS *(if any)*

Research Laboratories, Helsinki, Finland; University of California, Irvine, California; Laboratory of Clinical Studies, NIAAA; Laboratory of Clinical Sciences, NIMH

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Psychopharmacology

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1.0 | 0.33 | 0.67 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Combined gas chromatographic mass spectrometric methods previously developed for the assay of biogenic amines in various biological media have been employed to assess total body turnover of norepinephrine (sum NE) and dopamine (sum DA) in both human subjects and rats. We have also compared changes in sum NE and sum DA after a number of pharmacological manimpulations in rats. The aim of these animal studies was to gain an insight into how these pharmacological treatments influence brain catecholamines in depression, schizophrenia and hyperactive children.

(1) Consistent with our 1985 and 1986 Annual Reports, we have continued to gather additional supportive data that suggest a tendency for sum NE to be elevated in major depression. We have also observed a positive correlation between urinary-free cortico and urinary NE and VMA.

(2) Total body NE and DA turnover were assessed in both hyperactive children and adults after a number of pharmacological manipulations. The results indicated a correlation between therapeutic benefit and changes in both sum NE and DA irrespective of the direction of change.

(3) The effects of four commonly used antidepressant treatments on rat peripheral and central catecholamines were evaluated. A good correlation between the effects of these drugs and sum NE and sum DA in humans and rats was observed. It is suggested that because of this correlation, changes in the rat brain amines observed probably resemble the changes these treatments induce in the human brain. The four treatments employed were chronic zimelidine, desipramine, electroconvulsion and lithium.

(4) We are currently attempting to reproduce our initial study on DA and NE turnover in schizophrenia and hope to also include patients with tardive dyskinesia.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

## NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 MH 02261-03 NPB

PERIOD COVERED
October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Clinical Phenomena in Schizophrenia: Quantification in an Effort to Subtype

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*
Dr. Craig N. Karson, Staff Psychiatrist, NPB, IRP, NIMH

Dr. Llewellyn B. Bigelow, Associate Clinical Director, WAW Division, Saint Elizabeths Hospital, NIMH; Dr. Darrell G. Kirch, Senior Staff Fellow, NPB, DIRP, NIMH; Dr. Joel E. Kleinman, Chief, Section on Clinical Brain Studies, NPB, IRP, NIMH; Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH
Neuropsychiatry Branch

SECTION
Section on Clinical Neuropsychiatry

INSTITUTE AND LOCATION
NIMH, Saint Elizabeths Hospital, Washington, D.C.

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1.0 | 0.5 | 0.5 |

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project has been transferred to the Clinical Brain Disorders Branch.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

**NOTICE OF INTRAMURAL RESEARCH PROJECT**

PROJECT NUMBER

Z01 MH 02278-03 NPB

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Structural Brain Imaging in Schizophrenic Patients and Normal Subjects

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Daniel R. Weinberger, M.D., Chief, Sec. Clin. Neuropsychiatry, NPB, IRP, NIMH

Dr. George Jaskiw, Vis. Assoc., Sec. Clin. Neuropsychiatry, NPB, IRP, NIMH; Dr. Barbara Illowsky, Med. Staff Fellow, Sec. Clin. Brain Studies, NPB, IRP, NIMH; Dr. Dilip V. Jeste, Med. Officer, NPB, IRP, NIMH; Dr. Richard Jed Wyatt, Chief, NPB, IRP, NIMH; Dr. Allen Doran, Clin. Res. Assoc., Clin. Neurosci. Br., NIMH; Dr. Carl Feinstein, Asst. Prof. Psychiatry, George Washington Univ., Dr. David Pickar, Chief, Sec. Clinical Studies, Clin. Neurosci. Br., NIMH

COOPERATING UNITS *(if any)*

Clinical Neuroscience Branch, NIMH
George Washington University

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Clinical Neuropsychiatry

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 2.0 | 1.0 | 1.0 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project has been transferred to the Clinical Brain Disorders Branch.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02280-03 NPB

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Brain Tissue Transplantation in Primates

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

Richard Jed Wyatt, M.D., Chief, Neuropsychiatry Branch, IRP, NIMH

Dr. William J. Freed, Chief, Preclinical Neurosciences Section, NPB, IRP, NIMH;
Dr. Richard Nakamura, LPP, IRP, NIMH, Dr. Donald Price, Johns Hopkins Hospital;
Dr. Cheryl Kitt, Johns Hopkins Hospital

COOPERATING UNITS (if any)

LPP, NIMH
Johns Hopkins Hospital

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 2.5 | 1.0 | 1.5 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

To advance the work already performed in our laboratory with rats, adrenal medulla was grafted to the denervated caudate of the rhesus monkey in our continuing research on brain tissue transplantation. Success for graft survival has been good in the last year. An instrument (the brain grafter) which facilitates grafting was developed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02281-03 NPB

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Neural Tissue Microchip Interface

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

A. Paul Oliver, Physiologist, Neuropsychiatry Branch, IRP, NIMH

Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH; Dr. Myles Jaffe, Senior Staff Fellow, NPB, IRP, NIMH; Dr. Marty C. Peckerar, Naval Research Laboratory, Microelectronics Processing Facility, Washington, D.C.

COOPERATING UNITS *(if any)*

Naval Research Laboratory, Microelectronics Processing Facility, Washington, D.C.

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1.0 | 1.0 | 0 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

  ☐ (a1) Minors

  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The development of a neural prosthesis requires the fabrication of a solid state device capable of recording information from neural tissue and stimulating it in a timely manner. We began this process by designing a simpler system to test and monitor cultured neural tissue. To date we have identified problems such as suitable insulation for the device and some problems with corrosion in a critical part of the system. In addition we have improved the tissue culture system in an attempt to make the tests as realistic as possible. We have also worked with cultured retinal tissue in the system so that two way communication could be achieved.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

## NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 MH 02282-03 NPB

PERIOD COVERED
October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Neurovirology and Neuroimmunology of Schizophrenia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*
Darrell G. Kirch, M.D., Senior Staff Fellow, Neuropsychiatry Branch, IRP, NIMH

Dr. Rita Anand, Special Expert, NPB, IRP, NIMH; Dr. Anita Feenstra, Visiting Associate, NPB, IRP, NIMH; Dr. Nicholas M. Papadopoulos, Clinical Chemistry Service, NIH; Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

Clinical Chemistry Service, NIH

LAB/BRANCH
Neuropsychiatry Branch

SECTION
Section on Clinical Neuropsychiatry

INSTITUTE AND LOCATION
NIMH, Saint Elizabeths Hospital, Washington, D.C.

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1.0 | 0.5 | 0.5 |

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The project on neurovirology and neuroimmunology has continued its efforts to provide evidence that the pathogenesis of schizophrenia involves either an infectious process by a viral agent and/or an autoimmune reaction involving central nervous system tissue autoantibodies.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

## NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02309-02 NPB

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

The Brief Psychiatric Rating Scale as a Ward Daily Rating System

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Llewellyn B. Bigelow, M.D., Associate Clinical Director for the William A. White Division, Saint Elizabeths Hospital

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

| | | |
|---|---|---|
| TOTAL MAN-YEARS:<br>1.5 | PROFESSIONAL:<br>0.5 | OTHER:<br>1.0 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project has been transferred to the Office of the Clinical Director of DIRP, NIMH.

| | |
|---|---|
| DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE<br>**NOTICE OF INTRAMURAL RESEARCH PROJECT** | PROJECT NUMBER<br>Z01 MH 02310-02 NPB |

PERIOD COVERED
October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Treatment of Migraine with Anionic Polyelectrolytes

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*
Llewellyn B. Bigelow, M.D., Associate Clinical Director for the William A. White Division, Saint Elizabeths Hospital

Dr. Ernst Thonnard, General Medical Officer, Saint Elizabeths Hospital

COOPERATING UNITS *(if any)*

LAB/BRANCH
Neuropsychiatry Branch

SECTION
Office of the Chief

INSTITUTE AND LOCATION
NIMH, Saint Elizabeths Hospital, Washington, D.C.

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 0.5 | 0.5 | 0 |

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*
This project has been transferred to the Office of the Clinical Director of DIRP, NIMH.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 MH 02311-02 NPB

PERIOD COVERED
October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Ontogeny of Preprocholecystokinin, Proenkephalin and Tyrosine Hydroxylase in Rats

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*
Anne-Marie Duchemin, M.D., Visiting Fellow, Neuropsychiatry Branch, IRP, NIMH

Dr. Thanh Tam Quach, Visiting Associate, Neuropsychiatry Branch, IRP, NIMH; Dr. Michael Iadarola, Neurobiology-Anesthesiology Branch, NIDR, NIH; Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*
Neurobiology-Anesthesiology Branch, NIDR, NIH

LAB/BRANCH
Neuropsychiatry Branch

SECTION
Office of the Chief

INSTITUTE AND LOCATION
NIMH, Saint Elizabeths Hospital, Washington, D.C.

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 0.33 | 0.33 | 0 |

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Brain peptides are neurotransmitters or neuromodulators in the adult brain. In the embryonic brain, they may play a role in the organization and development of neurons and synaptogenesis. We studied the ontogeny of cholecystokinin (CCK) and enkephalin in the rat brain from day 12 prenatal to adulthood by measuring the peptides and the mRNA levels in parallel in the same tissues. CCK-immunoreactive peptides (CCK-IR) and enkephalin immunoreactive peptides (enkephalin-IR) were measured by using a specific radioimmunoassay. Messenger RNA levels were measured by blot hybridization of poly$(A)^+$ RNA with the corresponding cDNA probes. We also studied the ontogeny of tyrosine hydroxylase (TH), the limiting enzyme in the synthesis of noradrenaline and dopamine. The monoamines, their metabolites and the mRNA levels were measured comparatively in substantia nigra and locus ceruleus of the rat during development.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02312-02 NPB

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Neurotrophic Activity in Cerebrospinal Fluid of Schizophrenic Patients

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)*

Anne-Marie Duchemin, M.D., Visiting Fellow, Neuropsychiatry Branch, IRP, NIMH

Dr. Thanh Tam Quach, Visiting Associate, Neuropsychiatry Branch, IRP, NIMH; Dr. Charles Kaufmann, Staff Psychiatrist, Neuropsychiatry Branch, IRP, NIMH; Dr. Daniel Weinberger, Chief, Clinical Brain Disorders Branch, IRP, NIMH; Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 0.33 | 0.33 | 0 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

We used cultures of sympathetic neurons from chicken embryo ganglia as an assay for neurotrophic activity. Introduction of radioactive tracers has been developed to facilitate quantification of neurotrophic activity. We looked for neurotrophic activity in CSF of normal volunteers, neurologic and psychiatric patients. There was no evidence of neurotrophic activity in most of the CSF tested. However, CSFs of some schizophrenics were found able to support neuronal survival in culture. This activity was independent of neuroleptic treatment but was positively correlated with ventricular enlargement of the brain.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02313-02 NPB

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Retroviral Activity in Lymphocytes of Patients with Schizophrenia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Anita Feenstra, Ph.D., Visiting Associate, Neuropsychiatry Branch, IRP, NIMH

Dr. Darrell G. Kirch, Senior Staff Fellow, Neuropsychiatry Branch, IRP, NIMH; Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1.0 | 0.5 | 0.5 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The evidence that schizophrenia may involve infection by a virus (or viruses) has been indirect. This evidence includes the phenomenology of schizophrenia (insofar as it may be mimicked by some viral encephalitides), epidemiological factors (including a predominance among patients with late winter/early spring births, a north-south gradient, and occasional clustering of cases), and indirect laboratory evidence (gliosis in some neuropathological studies, spinal fluid protein abnormalities, and abnormalities in cell-mediated immunity).

The discovery of the human retroviruses, HTLVI, HTLVII and HIV, now also known to affect the CNS, together with the development of new techniques in human retrovirology, made it possible to investigate the role of this class of viruses in the etiology of schizophrenia.

Cultures of peripheral lymphocytes of patients with chronic schizophrenia were established and tested for the retrovirus-specific enzyme reverse transcriptase.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

**NOTICE OF INTRAMURAL RESEARCH PROJECT**

PROJECT NUMBER

Z01 MH 02314-02 NPB

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Development of an Auditory Sort Test

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Dr. Terry Goldberg, Special Expert, Neuropsychiatry Branch, IRP, NIMH

Dr. Daniel Weinberger, Chief, Section on Clinical Neuropsychiatry, NPB, IRP, NIMH; Dr. Craig Karson, Staff Psychiatrist, NPB, IRP, NIMH; Dr. Karen Berman, Staff Psychiatrist, NPB, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Clinical Neuropsychiatry

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 0.33 | 0.17 | 0.17 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project has been transferred to the Clinical Brain Disorders Branch.

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|---|---|
| **DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE**<br>**NOTICE OF INTRAMURAL RESEARCH PROJECT** | PROJECT NUMBER<br>Z01 MH 02315-02 NPB |

PERIOD COVERED
October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Hierarchy and Sensitivity in Putative Frontal Lobe Tasks

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*
Dr. Terry Goldberg, Special Expert, Neuropsychiatry Branch, IRP, NIMH

Dr. Daniel Weinberger, Chief, Section on Clinical Neuropsychiatry, NPB, IRP, NIMH;
Dr. John Kelsoe, Section on Clinical Studies, Clinical Neuroscience Branch, NIMH

COOPERATING UNITS *(if any)*
Section on Clinical Studies, Clinical Neuroscience Branch, NIMH

LAB/BRANCH
Neuropsychiatry Branch

SECTION
Section on Clinical Neuropsychiatry

INSTITUTE AND LOCATION
NIMH, Saint Elizabeths Hospital, Washington, D.C.

| | | |
|---|---|---|
| TOTAL MAN-YEARS:<br>0.33 | PROFESSIONAL:<br>0.17 | OTHER:<br>0.17 |

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*
This project has been transferred to the Clinical Brain Disorders Branch.

|  |  |
|---|---|
| DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE<br>**NOTICE OF INTRAMURAL RESEARCH PROJECT** | PROJECT NUMBER<br>Z01 MH 02316-02 NPB |

PERIOD COVERED
October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
"Teaching" the Wisconsin Card Sort to Schizophrenic Patients

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*
Dr. Terry Goldberg, Special Expert, Neuropsychiatry Branch, IRP, NIMH

Dr. Daniel Weinberger, Chief, Section on Clinical Neuropsychiatry, NPB, IRP, NIMH; Dr. Karen Berman, Staff Psychiatrist, NPB, IRP, NIMH; Dr. Marvin Podd, O'Malley Division, Saint Elizabeths Hospital

COOPERATING UNITS *(if any)*
O'Malley Division, Saint Elizabeths Hospital

LAB/BRANCH
Neuropsychiatry Branch

SECTION
Section on Clinical Neuropsychiatry

INSTITUTE AND LOCATION
NIMH, Saint Elizabeths Hospital, Washington, D.C.

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 0.33 | 0.17 | 0.17 |

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project has been transferred to the Clinical Brain Disorders Branch.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 MH 02317-02 NPB

PERIOD COVERED
October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Peripheral and Central Metabolism of D- and L-DOPA in Rats

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*
Farouk Karoum, Ph.D., Chemist, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH
Neuropsychiatry Branch

SECTION
Section on Psychopharmacology

INSTITUTE AND LOCATION
NIMH, Saint Elizabeths Hospital, Washington, D.C.

| | | |
|---|---|---|
| TOTAL MAN-YEARS:<br>1.0 | PROFESSIONAL:<br>0.33 | OTHER:<br>0.67 |

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The effects of administering deuterated L-DOPA on the formation and metabolism of peripheral and central non-deuterated catecholamines as described in the 1986 Annual Report is now completed. Our interest had shifted towards comparing central and peripheral metabolism of D-DOPA with that of L-DOPA.

We found that both D- and L-DOPA gave rise to DA by about the same efficiency. This unexpected finding led us to characterize these two amino acids biochemically as well as behaviorally. We also carried out additional experiments in order to explore the underlining mechanisms that are responsible for the formation of dopamine from D-DOPA.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02318-02 NPB

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Effects of Retinoic Acids on Brain, Behavior, and Drug Interactions

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Gregory M. Straw, M.D., Clinical Research Associate, Preclinical Neurosciences Section, NPB, IRP, NIMH

Dr. Darrell Kirch, Associate Clinical Associate, NPB, IRP, NIMH; Dr. William J. Freed, Chief, Preclinical Neurosciences Section, NPB, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Preclinical Neurosciences Section

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1.25 | 0.25 | 1.0 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project investigates the pathophysiology of retinoic acid action in vivo. Rats are the current model but expansion into mouse and guinea pig models is anticipated. The primary focus of the rat model is the assay of the pharmacokinetics of the interaction of 13-cis-retinoic acid with neuroleptics. Early results have shown statistically significant changes in the blood levels of haloperidol and one of its metabolites after the concurrent administration of 13-cis-retinoic acid to rats. Early results also suggest possible interactions with dopamine metabolism and opiate levels in the CNS.

PHS 6040 (Rev. 1/84)

GPO 914-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

**NOTICE OF INTRAMURAL RESEARCH PROJECT**

PROJECT NUMBER

Z01 MH 02320-02 NPB

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Magnetic Resonance Imaging (MRI) Studies

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Daniel R. Weinberger, M.D., Chief. Section on Clinical Neuropsychiatry, NPB, IRP, NIMH

Dr. Jean L. Cadet, Medical Staff Fellow, Section on Clinical Neuropsychiatry, NPB, IRP, NIMH; Dr. John Kelsoe, Medical Staff Fellow, Clinical Neuroscience Branch, NIMH; Dr. David Pickar, Chief, Section on Clinical Studies, CNB, IRP, NIMH

COOPERATING UNITS *(if any)*

Clinical Neuroscience Branch, NIMH; Section on Clinical Studies, CNB

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Clinical Neuropsychiatry

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 2.0 | 1.0 | 0.67 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project has been transferred to the Clinical Brain Disorders Branch.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02374-01 NPB

PERIOD COVERED
October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Clinical Trial of Isotretinoin in Schizophrenia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*
Gregory M. Straw, M.D., Medical Staff Fellow, Neuropsychiatry Branch, IRP, NIMH

Dr. Darrell G. Kirch, Senior Staff Fellow, NPB, IRP, NIMH; Dr. Myles Jaffe, Senior Staff Fellow, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH
Neuropsychiatry Branch

SECTION
Preclinical Neurosciences Section

INSTITUTE AND LOCATION
NIMH, Saint Elizabeths Hospital, Washington, D.C.

| | | |
|---|---|---|
| TOTAL MAN-YEARS:<br>0.25 | PROFESSIONAL:<br>0.25 | OTHER:<br>0 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Open clinical trials of isotretinoin in schizophrenic patients on and off of haloperidol have suggested a possibly beneficial synergism between haloperidol and isotretinoin in the treatment of psychotic illness. This has been supported by the results of animal studies of the direct and synergistic (with haloperidol) effects of isotretinoin on animal behavior. Therefore, this project has been initiated to evaluate these potential effects in a placebo controlled, double blind, cross over study. Also, other possible effects including changes in visual and auditory sensory processes will be monitored electrophysiologically.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

**NOTICE OF INTRAMURAL RESEARCH PROJECT**

PROJECT NUMBER

Z01 MH 02375-01 NPB

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Seasonality of Birth and Hospitalization for Schizophrenic Patients

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Pnncipal Investigator.) (Name, title, laboratory, and institute affiliation)*

Gregory M. Straw, M.D., Medical Staff Fellow, Neuropsychiatry Branch, IRP, NIMH

Dr. Guido Zami, Ph.D., Information Systems, Saint Elizabeths Hospital; Dr. James Lohr, Medical Staff Fellow, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Preclinical Neurosciences Section

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

| | | |
|---|---|---|
| TOTAL MAN-YEARS: 0.25 | PROFESSIONAL: 0.25 | OTHER: 0 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Many authors have reported seasonal variations in the evident birth rate and admission rate for schizophrenic patients. This project uses computerized hospital records and weather data to examine these possible "seasonal" effects.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01532-10 SMRP

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Regulation of Catecholamine Receptor

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | |
|---|---|---|
| De-Maw Chuang | Group Chief | LPP-NIMH |

COOPERATING UNITS *(if any)*

Carmine Coscia, St. Louis University Medical School
Graig Malbon, State University of New York at Stony Brook
Hannu Alho, Fidia Georgetown Neuroscience Institute

LAB/BRANCH

Laboratory of Preclinical Pharmacology

SECTION

Receptor Pharmacology Group

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Saint Elizabeths Hospital, Washington, D.C. 20032

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 0.4 | 0.4 | None |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The number of B-adrenergic receptor (BAR) fluctuates with changes in the neuronal activity in vivo. Two extremeties of this receptor plasticity are the supersensitivity and subsensitivity; the latter often involves the loss of receptor site, termed down-regulation. We have used a model system of frog erythrocyte to study the molecular mechanisms of B-receptor down-regulation induced by isoproterenol stimulation. Our previous studies have provided the first evidence that agonist-induced down regulation of BAR is associated with internalization of BAR sites in frog erythrocytes. This receptor internalization is causative for the desensitization of adenylate cyclase to BAR stimulation. Internalized BAR sites are sequestered in endocytotic vesicles with molecular weight more than $20 \times 10^6$ daltons and are recycled to the plasma membrane during receptor resensitization. Internalized BAR can be labeled by a lipophilic but not by a hydrophilic receptor ligand. Moreover, mechanisms of coated pit and coated vesicle may be involved in this receptor internalization and down-regulation. In the present study we have succeeded in staining BAR in frog erythrocytes using BAR specific antibody and detected important differences in the receptor staining pattern during receptor desensitization and down-regulation. Specifically, preceding the internalization of BAR, the staining of BAR on the plasma membrane by the BAR antibody was markedly enhanced. Internalization was associated with an increased labeling of a population of BAR which were unmasked by permeabilization of the cells with the detergent saponin. Currently we are attempting to elucidate the details of molecular events at the electron microscopic level using this morphological approach. Moreover, we have investigated whether BAR internalization occurs in the CNS. Purified coated vesicles isolated from bovine brain were found to contain BAR which was uncoupled to the GTP binding protein and adenylate cyclase. These BAR sites were labeled by a liphophilic ligand $^{125}$I-cyanopindolol but not by a hydrophilic ligand $^3$H-CGP-12177. This data suggest that BAR may be internalized by coated vesicle-mechanisms in the CNS. Thus, BAR internalization might play an important role in the CNS plasticity.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01555-07 SMRP

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Enkephalin Metabolism

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | |
|---|---|---|
| B. Mellstrom | Visiting Fellow | LPP-NIMH |
| H.-Y.T. Yang | Section Chief | LPP-NIMH |

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Preclinical Pharmacology

SECTION

Neuropeptide

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Saint Elizabeths Hospital, Washington, D.C. 20032

| | | |
|---|---|---|
| TOTAL MAN-YEARS: 0.4 | PROFESSIONAL: 0.4 | OTHER: 0 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project has been terminated because the prinicipal investigator has left.

| | |
|---|---|
| DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE<br>**NOTICE OF INTRAMURAL RESEARCH PROJECT** | PROJECT NUMBER<br>Z01 MH 01559-06 SMRP |

PERIOD COVERED
October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Phe-Met-Arg-Phe-$NH_2$ Like Peptides In The Brain And Spinal Cord: Function And Distributio

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | |
|---|---|---|
| H.-Y. T. Yang, Ph.D. | Section Chief | LPP-NIMH |
| E. A. Majane | Chemist | LPP-NIMH |
| A.M. Alho | Visiting Fellow | LPP-NIMH |

COOPERATING UNITS *(if any)*
1) Pertti Panula, M.D., Dept. of Anatomy, University of Helsinki, Finland
2) B.L. Roth, Surgical Research Division, Naval Medical Research Institute, Bethesda, MD

LAB/BRANCH
Laboratory of Preclinical Pharmacology

SECTION
Neuropeptide

INSTITUTE AND LOCATION
NIMH, ADAMHA, NIH, Saint Elizabeths Hospital, Washington, D.C. 20032

| | | |
|---|---|---|
| TOTAL MAN-YEARS:<br>2.0 | PROFESSIONAL:<br>1.2 | OTHER:<br>0.8 |

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

We have previously isolated from bovine brain and chemically characterized two putative endogenous opiate antagonist peptides. These peptides, Phe-Leu-Phe-Gln-Pro-Gln-Arg-Phe-$NH_2$ and Ala-Gly-Glu-Gly-Leu-Ser-Ser-Pro-Phe-Trp-Ser-Leu-Ala-Ala-Pro-Gln-Arg-Phe-$NH_2$, were found to be highly localized in periaqueductal gray and dorsal spinal cord, areas important for opiate antinociception. In this study, distribution and pathways of these two peptides in rat spinal cord were studied in detail by radioimmunoassay and immunohistochemistry. Levels of these two peptides are highest in dorsal gray and lowest in ventral white. After spinal cord transection, levels of these two peptides decreased significantly caudal to the transected region indicating the presence of descending pathways of these two peptides. Immunohistochemically, intense immunoreactivity was observed in substantia gelatinosa of posterior horn, scattered fibers were found in deeper laminae of posterior horn. The morphological study further suggests the possible role of these two peptides in opiate mediated analgesia.

In further studying the biological property of these two peptides, they were found to elevate mean arterial blood pressure. This pressor activity was attenuated by prior treatment with guanethidine or prazocin. The results suggest that these two peptides increase mean arterial pressure by potentiating the release of catecholamines.

The proposed course of this study is to investigate the mechanism by which these two peptides act to modulate opiate analgesia including release of these two peptides from spinal cord and receptors for these two peptides.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

**NOTICE OF INTRAMURAL RESEARCH PROJECT**

PROJECT NUMBER

Z01 MH 01577-04 SMRP

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Characterization of Serotonin Pre- and Postsynaptic Components in NCB-20 Cells

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | |
|---|---|---|
| J.-M. Cossery | Visiting Fellow | LPP-NIMH |
| X.-Z. Zhu | Visiting Fellow | LPP-NIMH |
| O. Dillon-Carter | Chemist | LPP-NIMH |
| D.-M. Chuang | Group Chief | LPP-NIMH |

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Preclinical Pharmacology

SECTION

Immunochemistry Group

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Saint Elizabeths Hospital, Washington, D.C. 20032

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1.6 | 1.6 | None |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

We have used NCB-20, a cloned cell line of mouse neuroblastoma and fetal chinese hamster brain cell, as a model system to study receptor interactions in the same cell. NCB-20 cells express serotonin (5-HT) receptors coupled to adenylate cyclase. We found that 5-HT and 5-methoxytryptamine activated adenylate cyclase in intact cells with low efficiency (EC$_{50}$ values ~500 nM), while some putative 5-HT$_{1A}$ receptor agonists, 8-hydroxy-2-(di-n-propylamino) tetralin or 8-OH-DPAT, ipsapirone and buspirone were ineffective. Receptor binding studies also showed that 5-HT was bound to NCB-20 cell membranes with low affinity, while vitrually no significant binding of 8-OH-DPAT was detected. These data suggest that 5-HT receptor coupled to adenylate cyclase in NCB-20 cells is distinct from 5-HT$_{1A}$ and may represent a novel class of receptors for 5-HT. We also found that NCB-20 cells are equipped with presynatic components of 5-HT neurons. These include a 5-HT uptake system and specific binding sites for imipramine which inhibits the uptake of 5-HT in a competitive manner. Addition of imipramine activated phosphosphoinositide hydrolysis catalyzed by phospholipase C. This activation was dose-and time-dependent and was nonadditive to that produced by carbachol. Moreover preexposure to imipramine induced a rapid desensitization to the response of imipramine and carbachol. Since NCB-20 cells possess multiple receptors coupled to different effector systems, this cell line is an usual system to study receptor cross-talks at the molecular levels.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

**NOTICE OF INTRAMURAL RESEARCH PROJECT**

PROJECT NUMBER

Z01 MH 01578-04 SMRP

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Expression of Genes for Insulin in Brain and Peripheral Tissues

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | |
|---|---|---|
| D.-M. Chuang | Group Chief | LPP-NIMH |
| T.T. Quach | Visiting Associate | NPB-NIMH |
| A.-M. Duchemin | Visiting Associate | NPB-NIMH |

COOPERATING UNITS *(if any)*

Neuropsychiatry Branch, NIMH

LAB/BRANCH

Laboratory of Preclinical Pharmacology

SECTION

Group of Immunochemistry

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Saint Elizabeths Hospital, Washington, D.C. 20032

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1.2 | 1.2 | None |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

It has been suggested that insulin-like proteins may be growth factors in the nerous systems. The aims of this project are to use a cDNA probe to detect the presence of mRNA for insulin or insulin-like peptide in extrapancreatic tissues including the brain and to investigate their physiological role. We extracted RNAs from various tissues using liquid nitrogen pulverization and by homogenization in the presence of GuSCN. The RNA pellets recovered from CsCl-cushion following centrifugation of the homogenate are subjected to oligo-dt columns for the purification of poly A$^{+}$RNAs which include mRNAs. These isolated mRNAs are electrophoresed on agarose gel followed by blotting to a nitrocellulose membrane. These immobilized mRNAs are then hybridized to a cloned cDNA fragment of proinsulin gene which has been nick-translated with $^{32}$P-dCTP. We found that the $^{32}$P-cDNA probe is hybridized to mRNA from extrapancreatic tissues under stringent conditions (i.e., high temperature and low salts). However, the molecular sizes of these hybridizable mRNA transcripts are different from that detected in the pancreas. Thus, the size of pancreatic mRNA is of 0.5 kilobase, whereas two major species of mRNA transcripts detected in the gut, heart and to a lesser extent, liver have approximately 4.2 and 2.2 kilobases. We also detected these two mRNA transcripts in the brain and a cloned cell line NCB-20 (neuroblastoma x fetal hamster brain cell hybrid), suggesting a neuronal location of these transcripts. Some minor mRNA species hybridizable to the cDNA probe were also found in the brain and other tissues. Thus, mRNA for insulin and insulin-like peptides can be detected in extrapancreatic tissues including the brain. We are current attempting to study the role of these insulin-like peptides in the growth, maturation and survival of neurons.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01579-04 SMRP

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Studies of an Endocoid for the $5HT_2$ Recognition Site

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | |
|---|---|---|
| B.L. Roth | Principal Investigator | Naval Medical Res. Inst. |
| D.-M. Chuang | Chemist | LPP-NIMH |
| X.-Z. Zhu | Visiting Fellow | LPP-NIMH |

COOPERATING UNITS *(if any)*

S. McLean, Laboratory of Neurophysiology, NIMH
B.L. Roth, Naval Medical Research Institute, Bethesda, MD

LAB/BRANCH

Laboratory of Preclinical Pharmacology

SECTION

Receptor Pharmacology Group

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Saint Elizabeths Hospital, Washington, D.C. 20032

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1.0 | 1.0 | None |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

$5HT_2$ receptors have low affinity for serotonin (5-HT) and do not show receptor supersensitivity following lesion of nerve ending. We have proposed for the existence of an endogenous ligand (endocoid) for this receptor site. Our previous studies have demonstrated that some protein fractions derived from bovine and rat brains display activity of inhibiting $^3$H-ketanserin binding but inhibiting only slightly $^3$H-mianserin binding to rat brain membrane. This protein (Mr=6000) has been partially purified by gel filtration and HPLC column chromatography.

The present studies show that two $^3$H-ketanserin recognition sites are present in rat striatum as revealed by autoradiography and nonlinear, least square regression algorythm. The high affinity site (Kd 0.4 nM) is similar to the $5\text{-}HT_2$ site previously characterized by various investigators. The low affinity site (Kd 20 nM) has a unique pharmacological specificity and is preferentially localized to rat striatum and septum. A series of conventional $5\text{-}HT_2$ receptor antagonists, 5-HT and 5-HT uptake blockers are ineffective at inhibiting $^3$H-ketanserin binding to this low affinity site. Also, chronic treatment with p-chlorophenylalanine, which deplets brain 5-HT, up-regulates only the high affinity site. Moreover, selective lesion of 5-HT nerve ending with a neurotoxin failed to affect this low affinity binding sites. Thus, in the striatum and septum, $^3$H-ketanserin labels a unique recognition site. This site has recently been shown to be associated with dopaminergic nerve endings and may regulate biogenic amine release through recognition by some endogenous ligand. The present findings may shed light on the role of this peptide endocoid in the modulation of neurotransmission.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

## NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01584-04 SMRP

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Noncompetitive Interactions Between Mu- and Delta-Opiate Receptors in Vitro

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | |
|---|---|---|
| Richard B. Rothman | Guest Researcher | LPP-NIMH |
| M. Herkenham | Staff Scientist | LNP-NIMH |
| S. McLean | Staff Fellow | LNP-NIMH |
| J. Cadet | Staff Scientist | NPB-NIMH |
| J. Byrd | Guest Researcher | LPP-NIMH |
| K. Rice | Staff Scientist | LC-NIDDK |
| V. Bykov | Student Volunteer | LPP-NIMH |

COOPERATING UNITS *(if any)*

B. Roth, Naval Medical Research Institute, Bethesda, MD
J. Holaday, Walter Reed Army Institute for Research, Washington, D.C.

LAB/BRANCH

Laboratory of Preclinical Pharmacology

SECTION

Neuropeptide

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Saint Elizabeths Hospital, Washington, D.C. 20032

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| | | |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
 ☐ (a1) Minors
 ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Work in my laboratory is directed towards testing a model of the opioid receptors sufficiently complex enough to explain varied physiological data. This model postuates a receptor complex consisting of adjacent and interacting mu, delta and kappa binding sites, as well as distinct mu, delta and kappa receptors not associated with the receptor complex.

To test this model we utilize several techniques: (1) quantitative ligand binding studies using the method of "binding surface analysis" and weighted nonlinear least squares curve fitting, (2) site-directed alkylating agents such as BIT (mu-directed), FIT (delta-directed) and beta-FNA (mu-directed), (3) receptor autoradiography to provide anatomical information, (4) "in vivo" manipulations such as chronic morphine and chronic naltrexone which up-regulate opiate receptors and (5) biochemical information using a technique to cross-link $^{125}$I-beta endorphin to opiate receptors.

As our work progress, not only is the model tested, but additional data is generated. Our work addresses fundamental issues of morphine tolerance and dependence. It has defined the opiate receptors labeled by ($^{3}$H) cycloFOXY, a novel antagonist suitable for position emission tomography. We have developed methods for measuring rat brain kappa receptors, a subtype of the opiate receptor implicated in eating disorders and work is underway to develop a kappa-directed site-directed alkylating agent.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

**NOTICE OF INTRAMURAL RESEARCH PROJECT**

PROJECT NUMBER

Z01 MH 01585-03 SMRP

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Molecular Mechanisms of Smooth Muscle Cell Contraction in Rat Aorta

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | |
|---|---|---|
| B.L. Roth | Guest Researcher | LPP, NIMH |
| T. Nakaki | Visiting Fellow | LPP, NIMH |
| D.-M. Chuang | Group Chief | LPP, NIMH |

COOPERATING UNITS *(if any)*

Naval Medical Research Institute, Surgical Res. Br., Bethesda, MD

LAB/BRANCH

Laboratory of Preclinical Pharmacology

SECTION

Group of Immunochemistry

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Saint Elizabeths Hospital, Washington, D.C. 20032

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1.4 | 1.4 | 0 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The smooth muscle of rat aorta was used as a model for the study of the molecular mechanisms of $5\text{-HT}_2$ receptor function. We have previously shown that 5-HT receptors in rat aorta are coupled to phosphoinositide (PI) - specific phospholipase C. Further, we showed that the mechanism of contraction elicited by 5-HT is a complicated scenario involving receptor-mediated activation of calcium channels and a phospholipase C. We now report that in rat aorta, the 5-HT-induced contraction and PI turnover are modulated by biologically active phorbol esters. In rat aorta, 5-HT stimulated PI turnover and contraction ($EC_{50}=10\pm3$ uM); these two responses were highly correlated ($r=0.95$; $P<.01$). We have characterized the inhibitory potency of a variety of 5-HT-antagonists against the stimulation of PI turnover elicited by 5-HT. Classic $5\text{-HT}_2$ antagonists mianserin, ketanserin, metergoline and pizotifen were found to inhibit this response in the low nanomolar range; amitryptiline and haloperidol were 10- to 20- fold less potent. The alpha-1 receptor antagonist, prazosin, was inactive in micromolar concentrations. The potency of the $5\text{-HT}_2$ antagonists was correlated with their ability to displace $[^3H]$ketanserin binding from rat frontal cortex membranes ($r=0.90$; $P<.05$). The tumor promoter phorbol dibutyrate was found to inhibit 5-HT-stimulated PI turnover at low nanomolar concentrations whereas the biologically inactive substance 4-α-phorbol was ineffective. Pretreatment of rat aorta with phorbol dibutyrate at concentrations that inhibited 5-HT-induced PI turnover also attenuated the aortic contraction induced by 5-HT in the presence of a calcium channel blocker nitrendipine. Our results suggest that phorbol esters may densensitize $5\text{-HT}_2$-receptor-mediated PI turnover and contraction of rat aorta, possibly via an activation of protein kinase C.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02298-02 SMRP

PERIOD COVERED
October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Receptor Regulation in Cultured Cerebellum Granule Cells

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)*

| | | |
|---|---|---|
| Xing-Zu Zhu | Visiting Fellow | LPP-NIMH |
| Ora Dillon-Carter | Chemist | LPP-NIMH |
| Jian Xu | Visiting Fellow | LPP-NIMH |
| De-Maw Chuang | Group Chief | LPP-NIMH |

COOPERATING UNITS *(if any)*

None

LAB/BRANCH
Laboratory of Preclinical Pharmacology

SECTION
Group on Receptor Pharmacology

INSTITUTE AND LOCATION
NIMH, ADAMHA, NIH, Saint Elizabeths Hospital, Washington, D.C. 20032

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1.2 | 1.2 | 0 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Primary culture of cerebellar granular cells was prepared fron 8-day old Sprague Dawley rats. We found that these cells possess adrenergic $\alpha_1$, histaminergic $H_1$, 5-$HT_2$ and muscarinic cholinergic receptors linked to phospholipase C. The response of muscarinic receptors stimulated by carbachol was particurlaly robust; this receptor agonist increased by about 30-fold the hydrolysis of phosphoinositide hydrolysis measured by the accumulation of inositol monophosphate ($IP_1$) in the presence of lithium. This muscarinic receptor response can be desensitized by pretreatment with carbachol or oxotremorine, another muscarinic receptor agonist. This receptor desensitization can be dissected into fast and slow components. The fast component is complete within one hr of stimulation and appears to involve receptor uncoupling. The slow component involves receptor loss assessed by using $^3H$-QNB and $^3H$-N-methyl-scopolamine (NMS) as the receptor ligand. The responses of adrenergic $\alpha_1$, histaminergic $H_1$ and 5-$HT_2$ receptors can also be desensitized by stimulation with their respective agonist. However, no heterologous desensitization was found when these receptors were stimulated with their selective agonist for as long as 18 hrs. Cerebellar granular cells also express $GABA_B$ receptor which is linked to inhibition of adenylate cyclase. We found that stimulation of these $GABA_B$ receptors leads to inhibition of voltage sensitive calcium uptake. Moreover, inhibition of this calcium uptake appears to result in attenuation of the release of preloaded D-aspartate from granule cells. These results suggest that voltage sensitive calcium channel rather than the receptor-coupled phospholipase C system plays a major role in regulating the release of the excitatory neurotransmitter from granule cells.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02299-02 SMRP

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT (*80 characters or less. Title must fit on one line between the borders.*)

Receptor-Mediated Phosphoinositide Turnover

PRINCIPAL INVESTIGATOR (*List other professional personnel below the Principal Investigator.*) (*Name, title, laboratory, and institute affiliation*)

| | | |
|---|---|---|
| De-Maw Chuang | Group Chief | LPP-NIMH |
| Ora Dillon-Carter | Chemist | LPP-NIMH |

COOPERATING UNITS (*if any*)

None

LAB/BRANCH

Laboratory of Preclinical Pharmacology

SECTION

Group on Receptor Pharmacology

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Saint Elizabeths Hospital, Washington, D.C. 20032

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1.2 | 1.2 | None |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK (*Use standard unreduced type. Do not exceed the space provided.*)

This investigation aims at the role and regulation of receptor-coupled phospholipase C. We found that in a clonal neurotumor hybrid NCB-20, these cells expresses a variety of receptors of neurotransmitters and neuromodulators that are coupled to phosphoinositide (PI) hydrolysis. Carbachol, a muscarinic cholinergic receptor agonist markedly increased the accumulation of inositol monophosphate (IP$_1$) in the presence of lithium (Li$^+$). This increase was time and dose dependent. The formations of inositol bisphosphate and trisphosphate were also increased by this agonist but to a lesser extent and with a faster time course. Antagonist specificity suggests that this effect is mediated by the M$_1$, cholinergic receptors. This activation was associated with a rapid increase in the efflux of $^{45}$Ca from cells. NCB-20 cells also contain histamine-sensitive PI turnover system. Antagonist effect indicated that this is a histamine H$_1$ receptor-mediated response. The neuropeptide, bradykinin, also caused a robust (more than 10-fold) increase of $^3$H-IP$_1$ accumulation. The effects of bradykinin, histamine and carbachol were additive to each other. The carbachol-induced $^3$H-IP$_1$ accumulation was completely inhibited by veratridine at concentrations that inhibit the voltage-sensitive sodium channel. The basal accumulation was increased 2-fold by veratridine, while the activities increased by histamine and bradykinin were unaffected. The responses of both bradykinin and carbachol were desensitized by preexposure to bradykinin and carbachol, respectively. Biologically active phorbol esters markedly attenuated the bradykinin and carbachol-receptor mediated responses and significantly inhibited the basal phospholipase C activity, suggesting that either phospholipase C or some phospholipase C regulatory proteins are substrates of phorbol ester-activated protein kinase C. Pertussis toxin only attenuated in part the carbachol and bradykinin-induced PI turnover. The concentration of lithium required to maximally increase the receptor-activated $^3$H-IP$_1$ accumulation in cultured NCB-20 cells was about 60-80 mM which was about 10-time greater than those found in brain slices and other neurotumor cell lines such as NG 108-15 neurohybrid. This unusual requirement of high lithium may suggest that NCB-20 cells express a novel type of inositol-1-phosphatase and might lead to some clinical implication for the mechanisms of the therapeutic effect of lithium in the treatment of manic depression.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02300-02 SMRP

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Regulation of Neurotransmitter Receptors by Cell Differentiation

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | |
|---|---|---|
| Xing-Zu Zhu | Visiting Fellow | LPP-NIMH |
| De-Maw Chuang | Group Chief | LPP-NIMH |

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Preclinical Pharmacology

SECTION

Receptor Pharmacology Group

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Saint Elizabeths Hospital, Washington, D.C. 20032

| TOTAL MAN-YEARS | PROFESSIONAL. | OTHER. |
|---|---|---|
| 1.2 | 1.2 | None |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The understanding of the molecular mechanisms of the differentiation of neurons during development is of fundamental importance in neuroscience. We have used two neuronal hybridomas, NCB-20, and NG108-15 cells, to study the receptor regulation induced by two differentiation promoters, dibutyryl cAMP ($Bt_2cAMP$) and butyrate. Exposure of cells to $Bt_2cAMP$ caused a time and dose dependent decrease in the binding to muscarinic acetylcholine, adrenergic $\alpha_2$ and opioid $\delta$ receptors. The loss of muscarinic cholinergic receptor site assessed by using $^3$H-QNB as the binding ligand was about 40% of the control; this decrease was associated with an attenuation of the carbachol-induced phosphoinositide hydrolysis. The maximal decreases of adrenergic $\alpha_2$ and opioid $\delta$ receptor binding were about 80% when $^3$H-clonidine and $^3$H-D-Ala-D-Leu-enkephalin (DADLE) were used as their respective ligands. In contrast, butyrate induced a time and dose dependent increase in the opioid receptor binding sites. The maximal increase was about 300% of the control when 1 mM of butyrate was added to the culture for 72 hrs. The up-regulation of opioid receptor resulted in an increased potency of DADLE in inhibiting adenylate cyclase activity. Similar butyrate treatment up-regulated muscarinic receptors by 100% and increased carbachol-induced phosphoinositide by about 200%. Long term butyrate treatment of NG108-15 cells did not change muscarinic and opioid receptor binding but induced a 100% increase of the density of $\alpha_2$-adrenergic receptors. Butyrate treatment induced cell morphological changes which were distinct from those induced by $Bt_2cAMP$. These results suggest that these two differentiation agents can either up-regulate or down-regulate neurotransmitter receptor proteins. Moreover, up-regulation of neurotransmitter receptors induced by butyrate may involve concerted interactions of genetic factors derived from both parents of these two neurohybrids.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

## NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02301-02 SMRP

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Functional Role of Adrenal NPY

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

| | | |
|---|---|---|
| H.-Y. T. Yang | Section Chief | LPP-NIMH |
| E. A. Majane | Chemist | LPP-NIMH |

COOPERATING UNITS *(if any)*

Terry D. Hexum, PH.D., Associate Prof., Dept. of Pharmacology, University of Nebraska, Medical Center, Omaha, Nebraska

LAB/BRANCH

Laboratory of Preclinical Pharmacology

SECTION

Neuropeptide

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Saint Elizabeths Hospital, Washington, D.C. 20032

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 2.0 | 1.2 | 0.8 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

High concentrations of neuropeptide Y have been found in many norepinephrine containing chromaffin cells in adrenal glands of various species. Adrenal gland seems to provide an interesting model system in which to investigate the functional role of NPY because evidence is accumulating that NPY may have modulatory effect on catecholamine. Previously, we have found that NPY can be released from bovine adrenal by acetylcholine. In the present study, the cholinergic receptor mediated secretion was further characterized by using retrogradedly perfused bovine adrenal glands. Infusion of acetylcholine produced a dose dependent increase in NPY secretion. Hexamethonium antagonized this NPY release whereas atropine did not. The role of the nicotinic cholinergic receptor in this process was further established by examining the effect of 1,1-dimethyl-4-phenlpiperazinium (DMPP). Infusion of DMPP also stimulated the NPY secretion. Biochemical analysis by HPLC revealed that four NPY immunoreactive peptides were secreted and the major immunoreactivity was identified to be authentic NPY. This release pattern of NPY is similar to that of catecholamines, thus it may be suggested that NPY is co-released with catecholamines by exocytosis via stimulation of nicotinic receptor. Previously, we have found that NPY levels in rat adrenal glands increase markedly with age during maturation and furthermore, an additional NPY-like peptide is detected in adrenal glands of older rats but not in that of younger rats. The nature of this NPY-like peptide is presently unclear; however, further characterization of this NPY-like peptide indicates that it is not an oxidized form of NPY, PYY or a degraded fragment of NPY. Furthermore, this NPY-like peptide is present in splanchnic nerves and also in chromaffin cells and can be secreted upon stimulation of cholinergic receptor. Highly purified NPY-like material has been prepared from bovine adrenal glands and we are planning to examine the biological activity of this new peptide. It is known that NPY exerts direct vasopressor effect and potentiates catecholamine induced vasoconstriction; furthermore, NPY can be co-released with catecholamines from adrenal glands thus NPY may contribute to the cardiovascular effects seen upon adrenal activation.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

**NOTICE OF INTRAMURAL RESEARCH PROJECT**

PROJECT NUMBER

Z01 MH 02378-01 SMRP

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Histochemical Localization of Phe-Leu-Phe-Gln-Pro-Gln-Arg-Phe-NH$_2$ Immunoreactivity in Mammalian CNS

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)*

| | | |
|---|---|---|
| T. Salminen | Visiting Fellow | LPP-NIMH |
| E.A. Majane | Chemist | LPP-NIMH |
| H.-Y.T. Yang | Pharmacologist | LPP-NIMH |

COOPERATING UNITS *(if any)*

C.-H. Lee, Naval Medical Research Institution, Bethesda, Maryland

LAB/BRANCH

Laboratory of Preclinical Pharmacology

SECTION

Section on Neuropeptides

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Saint Elizabeths Hospital, Washington, D.C. 20032

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 1.0 | 0.6 | 0.4 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The tetrapeptide phe-met-arg-phe-NH$_2$ (FMRF-NH$_2$) was originally isolated from macrocallista nimbosa clam and subsequently existence of FMRF-NH$_2$-like peptides in mammalian CNS was demonstrated by the antiserum raised against FMRF-NH$_2$. Recently, two of these FMRF-NH$_2$-like peptides were isolated from bovine brain and chemically characterized. In this study, monoclonal antibody against one of these FMRF-NH$_2$-like peptides of mammalian origin, phe-leu-phe-gln-pro-gln-arg-phe-NH$_2$ (F-8-F-NH$_2$), was generated and will be used to study the distribution of F-8-F-NH$_2$ in detail by immunohistochemical technique. By using F-8-F-NH$_2$ conjugated to hemocyanin as antigen, three murine monoclonal antibodies of IgG isotype were produced through cell fusion and cloning. The specificity study indicated that those antibodies cross-reacted with peptides having arg-phe-NH$_2$ at their c-termini but showed no cross-reaction with NPY, PYY or met$^5$-enk-arg$^6$phe$^7$. The result indicates that these monoclonal antiodies will enable us to carry out the immunohistochemical localization of F-8-F-NH$_2$ or FMRF-NH$_2$ immunoreactivity and compare this distribution with the distribution of NPY. Some immunohistochemical studies using polyclonal antiserum indicate that it is difficult to distinguish between mammalian FMRF-NH$_2$-like immunoreactivity from NPY due to cross-reactions of antisera. Extracts from spinal cord was analyzed by high pressure liquid chromatography coupled with radioimmunoassay using the monoclonal antibody. The major immunoreactivity was identified as F-8-F-NH$_2$ and NPY was not recognized by the antibody, thus the specificity of the monoclonal antibody was further confirmed. In the periaqueductal gray area, the preliminary study using the monoclonal antibody showed numerous immunoreactive nerve fibers around blood vessels and capillaries. Network of F-8-F-NH$_2$ positive nerve fibers was found surrounding the cerebral aqueduct and running in the epithelium. We plan to extend this immunohistochemical study to other regions of CNS and hope to provide a frame work for further understanding of possible function of F-8-F-NH$_2$ or mammalian FMRF-NH$_2$-like peptides.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

## NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02316-02 CBDB

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

"Teaching the Wisconsin Card Sort of Schizophrenic Patients

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator ) (Name, title, laboratory, and institute affiliation)

Dr. Terry Goldberg, Special Expert, Clinical brain Disorders Branch

Dr. Daniel Weinberger, Chief, Section on Clinical Brain Disorders Branch NPB, IRP, NIMH; Dr. Karen F. Berman, Staff Psychiatrist, NPB, IRP, NIMH; Dr. Marvin Podd, O'Malley Division, Saint Elizabeths Hospital

COOPERATING UNITS (if any)

O'Malley Division, Saint Elizabeths Hospital

LAB/BRANCH

Clinical Brain Disorders Branch

SECTION

Section on Clinical Studies

INSTITUTE AND LOCATION

NIMH, WAW Bldg., Saint Elizabeths Hospital

| | | |
|---|---|---|
| TOTAL MAN-YEARS: .33 | PROFESSIONAL: .33 | OTHER: 0 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This Project has been completed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02351-01 CBDB

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Pathology of Selected Central Nervous System Degenerative Disorders

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Dr. M.F. Casanova, Neurologist and Neuropathologist, NIMH

Dr. D. Price, Director Neuropathology Laboratory, Johns Hopkins University, Dr. G. Moore, Assistant Professor of Pathology, Johns Hopkins University, Dr. L. Cork, Associate Professor of Veterinary Medicine, Johns Hopkins University, Dr. R. Struble, Instructor of Pathology, Johns Hopkins University, Dr. P. Whitehouse, Associate professor, Case Western University.

COOPERATING UNITS *(if any)*

Clinical Brain Disorders Branch, NIMH; Neuropsychiatry Branch, NIMH.

LAB/BRANCH

Clinical Brain Disorders Branch

SECTION

Section On Neuropathology Studies

INSTITUTE AND LOCATION

NIMH, WAW Bldg., St. Elizabeths Hospital

| | | |
|---|---|---|
| TOTAL MAN-YEARS: 1 | PROFESSIONAL: 3 | OTHER: 0 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Selected neuropsychiaric conditions (Alzheimer's Disease (AD), Schizophrenia (SC), Dystonia musculorum deformans (DMD) and Progressive Supranuclear Palsy (PSP) were studied with quantitative anatomical techniques in order to establish clinico-pathological correlates and ellucidate pathogenesis. The structures incriminated by our research were further studied during gestation to discern possible developmental insults which could give rise to these neuropsychiatric conditions.

A. In AD: We described sequestration of tubulin in granulovacuolar degeneration and the involvement of various neuropeptidergic systems in the abnormal neurites surrounding plaques.

B. In DMD: We provided the first report of pathology involving various brainstem structures.

C. In PSP: We described cell loss in a major cholinergic non-motor nuclei in the brainstem.

D. In SC: We reviewed a published report on astrocytosis but could not confirm their findings.

The significance of the project lies in the identification of pathological correlates to these neuropsychiatric conditions as a first step towards the discovery of their etiology and possible therapeutic interventions.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

## NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02352-02 CBDB

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Prefrontal Cortical Modulation Of Subcortical Dopamine Systems

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Dr. George Jaskiw, Clinical Brain Disorders Branch, NIMH; Dr. Farouk Karoum, Neuropsychiatry Branch, NIMH; Dr. William Freed, Neuropsychiatry Branch, NIMH; Dr. Joel Kleinman, Clinical Brain Disorders Branch, NIMH; Dr. Daniel Weinberger, Clinical Brain Disorders Branch, NIMH.

COOPERATING UNITS *(if any)*

Clinical Brain Disorders Branch, NIMH; Neuropsychiatry Branch, NIMH.

LAB/BRANCH

Clinical Brain Disorders Branch

SECTION

Section On Clinical Studies

INSTITUTE AND LOCATION

NIMH, WAW Bldg, St. Elizabeths Hospital

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 8 | 1 | 0 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

We have examined the relationships between catecholamine systems in the prefrontal cortex (PFC) and subcortical areas, notably the nucleus accumbens and corpus striatum. Our work suggests that chemical lesioning of efferents from the prefrontal cortex to subcortical areas does not markedly alter behaviors such as stereotypy and locomotion, believed to be mediated by dopamine systems in the latter. Along with other work, this suggests that dopamine afferents to prefrontal cortex play a unique role in modulating subcortical dopamine systems.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02353-02 CBDB

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Cranial Asymmetries And The Reliability Of The International 10-20 System

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Principal Investigator: Michael Myslobodsky, M.D., Clinical Brain Disorders Branch, NIMH

Others: Richard Coppola, D.Sc., Clinical Brain Disorders Branch, NIMH, Craig Karson, M.D., Clinical Brain Disorders Branch, NIMH, David Daniel, M.D., Clinical Brain Disorders Branch, NIMH, Daniel R. Weinberger, M.D., Chief, Clinical Brain Disorders Branch, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Brain Disorders Branch

SECTION

Section on Clinical Studies

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

| | | |
|---|---|---|
| TOTAL MAN-YEARS: .1 | PROFESSIONAL: 3 | OTHER: 0 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

We have found that inconspicuous cranial asymmetry may covary with the lateral distribution of the EEG. Occipital flattening correlated with increased alpha in the subdominant parietal and central leads and increased beta power in caudal dominant leads. Frontal asymmetry ("frontal buldging") correlated with a relative increase of delta over the midline and the dominant parieto-occipital leads, with a generalized increase in alpha power, and with increased beta in dominant parietal and central leads. This study suggests that it might be desirable to verify electrode positions on the head on the basis of CT-MRI findings in all cases where brain laterality is at issue.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02354-01 CBDB

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Amphetamine and Frontal Lobe Functioning in Schizophrenia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Principal Investigator: Terry Goldberg, Ph.D., Special Expert, CBDB, IRP, NIMH

Others: Joel E. Kleinman, M.D., Ph.D., Deputy Chief, CBDB, IRP, NIMH; Llewellyn B. Bigelow, M.D., Associate Clinical Director, WAW Building, St. Elizabeths Hospital, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Brain Disorders Branch

SECTION

Section on Clinical Studies

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

| | | |
|---|---|---|
| TOTAL MAN-YEARS: .33 | PROFESSIONAL: .33 | OTHER: 0 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Research on the effects of amphetamine in schizophrenia is conflicting. It is known that amphetamine may cause paranoid psychosis. On the other hand, transitory improvement in some patients given acute doses of amphetamine has been reported. It is reasonable to speculate that negative symptoms of schizophrenia, such as anergia, lack of motivation, flattened affect, and poor planning may be amenable to such treatment. In addition, patients with schizophrenia generally do poorly on neuropsychological tests thought to assess frontal lobe functioning. We therefore propose a pharmacological strategy involving the administration of amphetamine in the hope that this drug may reverse some of the abnormalities found in chronic schizophrenia, whether they be symptomatic or cognitive.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02355-01 CBDB

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Autism: A Study of Cerebrophysiology, Neuroanatomy and Neuropsychology

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Principal Investigator: Terry Goldberg, Ph.D., Special Expert, CBDB, IRP, NIMH

Others: Daniel R. Weinberger, M.D., Chief, CBDB, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Brain Disorders Branch

SECTION

Section on Clinical Brain

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

| | | |
|---|---|---|
| TOTAL MAN-YEARS:<br>.33 | PROFESSIONAL:<br>.33 | OTHER:<br>0 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Few studies have employed multimodal measurements in the same autistic individual, thus considerably reducing their power. The current proposal will attempt to use cerebral blood flow, magnetic resonance imaging, and neuropsychology to provide convergent evidence as to the source of the deficit in autism. In this study, autistic individuals would be presented with cognitive tasks and affect laden tasks in order to challenge various brain regions. Activation will then be correlated with brain structures that were imaged on MR scans as well as results of neuropsychological tests tapping attention, memory, procedural abilities, language, and visual spatial functions. By utilizing autistic individuals with savant skills, we hope not only to gain greater understanding of the neurobiology of exceptional performance, but increased "signal-to-noise" ratio in the autistic population. Autistic individuals without savant skills and mentally retarded individuals, as well as normals, will serve as controls.

| | |
|---|---|
| DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE<br>**NOTICE OF INTRAMURAL RESEARCH PROJECT** | PROJECT NUMBER<br>Z01 MH 02356-01 CBDB |

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Procedural and Problem Solving Abilities in Schizophrenic Patients

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Principal Investigator: Terry Goldberg, Ph.D., Special Expert, CBDB, IRP, NIMH

Others: Jean St.-Cyr, Ph.D., Visiting Scientist, Neuropsychology Lab., IRP, NIMH;
Daniel R. Weinberger, M.D., Chief, CBDB, IRP, NIMH

COOPERATING UNITS *(if any)*

Neuropsychology Laboratory, NIMH

LAB/BRANCH

Clinical Brain Disorders Branch

SECTION

Section on Clinical Studies

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| .33 | .33 | 0 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☒ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Certain tasks that come under the rubric of procedural may be learned by subjects with various organic disorders who otherwise have marked difficulty recalling new information over time. One such tasks is called Tower of Hanoi. It involves moving discs from one peg to another. As well as a procedural component, it also involves problem solving and has been used as a model for conscious problem solving in artificial intelligence. It is thought that the neural system which mediates procedural performance (the basal ganglia) is distinct from the system that is involved in higher level problem solving (prefrontal) or everyday long term memory for items (diencephalic and medial temporal). Two versions of the Tower of Hanoi were administered to schizophrenic patients as well as a control task that involved higher level visual spatial processing. In addition, efforts were made to teach both tasks to patients who experienced difficulty.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02357-02 CBDB

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Recall and Recognition Memory in Schizophrenia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Principal Investigator: Terry Goldberg, Ph.D., Special Expert, CBDB, IRP, NIMH

Others: Daniel R. Weinberger, M.D., Chief, CBDB, IRP, NIMH; Neil H. Pliskin, M.A., William A. White Division, IRP, NIMH; Karen F. Berman, M.D., Staff Psychiatrist, CBDB, IRP, NIMH; Marvin Podd, Ph.D., Director of Training, Psychology, Bethesda Naval Hospital

COOPERATING UNITS *(if any)*

Bethesda Naval Hospital

LAB/BRANCH

Clinical Brain Disorders Branch

SECTION

Section on Clinical Studies

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| .33 | .33 | 0 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

It is well known that memory deficits exist in schizophrenia. However, it has been difficult to characterize them. Using the Selective Reminding memory test, 31 schizophrenic patients were assessed on their ability to learn a word list over 12 successive trials (processing which involves acquisition, maintenance and retrieval). These results were compared to recognition memory (in which retrieval or recall factors are minimized) for the word list. Retrieval was differentially impaired and was found to correlate significantly with an anergia factor on the Brief Psychiatric Rating Scale. The latter may be an index of dopaminergic "push." In fact, the profile was consistent with frontal lobe patients who are considered to suffer from the "forgetting to remember" syndrome.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02358-02 CBDB

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Atheoretical Multivariate Statistical Techniques

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Principal Investigators: Terry Goldberg, Ph.D., Special Expert, CBDB, IRP, NIMH

Others: Daniel R. Weinberger, M.D., Chief, CBDB, IRP, NIMH; Neil H. Pliskin, M.A., Staff Psychologist, William A. White Division, IRP, NIMH, Karen F. Berman, M.D., Staff Psychiatrist, CBDB, IRP, NIMH; Marvin Podd, Ph.D., Director of Training, Psychology, Bethesda Naval Hospital

COOPERATING UNITS *(if any)*

Bethesda Naval Hospital

LAB/BRANCH

Clinical Brain Disorders Branch

SECTION

Section on Clinical Studies

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| .33 | .33 | 0 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Multivariate data reduction techniques have recently become available through statistical computer packages. Through both factor analysis and cluster analysis, variables and cases respectively may be aggregated. These techniques were applied to a sample of schizophrenic patients who had received the Wisconsin Card Sort. In the latter study, data that were based on means were employed. However, the approach might have obscured distinct subtypes. Therefore, we attempted to cluster patients based on performance. However, we found that even small changes in the statistical programs led to major differences in the solutions we derived.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

## NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02359-01 CBDB

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Age Disorientation, Mental Status, and Ventricular Brain Ratio

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Principal Investigator: Terry Goldberg, Ph.D., Special Expert, CBDB, IRP, NIMH

Others: Joel E. Kleinman, M.D., Ph.D., Deputy Chief, CBDB, IRP, NIMH; Michael S. Myslobodsky, M.D., Visiting Scientist, CBDB, IRP, NIMH; David G. Daniel, M.D., Medical Staff Fellow, CBDB, IRP, NIMH; Daniel R. Weinberger, M.D., Chief, CBDB, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Brain Disorders Branch

SECTION

Section on Clinical Studies

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

| | | |
|---|---|---|
| TOTAL MAN-YEARS: .33 | PROFESSIONAL: .33 | OTHER: 0 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

A sizable minority of schizophrenic patients are age disoriented, that is, they do not know their own chronologic age. This special type of impairment was not found to be associated with enlarged cerebral ventricles by another group. However, the mean age of their group was old and they did not distinguish patients delusional for their age from patients demented and age disoriented. We assessed a younger sample and separated age delusional from age disoriented demented patients and found a significant difference in ventricular-brain ratio (VBR) between age oriented and age disoriented/demented patients.

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| DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE<br>NOTICE OF INTRAMURAL RESEARCH PROJECT | PROJECT NUMBER<br>Z01 MH 02388-02 CBDB |

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Regional Cerebral Blood Flow in Neuropsychiatric Patients and in Normal Subjects

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Principal Investigators: Daniel R. Weinberger, M.D., Chief, Clinical Brain Disorders Branch, IRP, NIMH and Karen Faith Berman, M.D., Staff Psychiatrist, Clinical Brain Disorders Branch, IRP, NIMH

Others: Douglas Jones, Ph.D., Physicist, Clinical Brain Disorders Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Brain Disorders Branch

SECTION

Section on Clinical Studies

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 4.25 | 2.25 | 2 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Using the Xenon133 inhalation technique, the regional cerebral blood flow (rCBF) lab within the Clinical Brain Disorders Branch carries out investigations of rCBF (as an indicator of regional cortical metabolism) in a variety of neuropsychiatric patients and in normal subjects. Patient populations, including those with chronic schizophrenia, affective disorder, obsessive-compulsive disorder, Huntington's disease, Parkinson's disease, Alzheimer's disease, and dyslexia are studied before and during various exploratory and therapeutic interventions. Normal control subjects matched for each patient study are investigated concurrently. Cortical metabolic concomitants of states of normal cognition and consciousness are also being explored. The Xenon133 method allows for multiple determinations of rCBF in a single individual who can thus serve as his or her own control while being studied serially under various cognitive and/or medication conditions. This allows paradigms to be designed to specifically test hypotheses about regional cortical function in disease states and normal higher cognitive function, and to specifically monitor experimental and therapeutic interventions in neuropsychiatric disorders. Careful and creative application of this versatile tool has produced important results. Experiments tailored to explore dorsolateral prefrontal cortex (DLPFC), an area of special interest in schizophrenia, have shown this area to be de-activated in patients with schizophrenia under conditions of cognitively specific, regionally selective demand upon this area - conditions under which normals increase metabolism in DLPFC. In contrast Huntington's disease patients, who are as cognitively impaired as schizophrenics, do not show DLPFC rCBF abnormality, but rather rCBF patterns similar to normal subjects. This is important evidence for the existence of subcortical dementia, which, until now, has been questioned by some.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02389-02 CBDB

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Brain Electrical Activity Mapping in Neuropsychiatric Patients

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Principal Investigator: Craig N. Karson, M.D., Staff Psychiatrist, Clinical Brain Disorders Branch, IRP, NIMH

Others: Terry Goldberg, Ph.D., Special Expert, CBDB, IRP, NIMH; Karen F. Berman, M.D., Staff Psychiatrist, CBDB, IRP, NIMH; Ralph Fawcett, M.D., Medical Staff Fellow, NPB, IRP, NIMH, Richard Coppola, D.Sc., Senior Engineer Officer, CBDB, IRP, NIMH; Daniel R. Weinberger, M.D., Chief, CBDB, IRP, NIMH

COOPERATING UNITS *(if any)*

Neuropsychiatry Branch, NIMH

LAB/BRANCH

Clinical Brain Disorders Branch

SECTION

Section on Clinical Studies

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 2 | .5 | .5 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

We have confirmed that patients with schizophrenia have an increase of slow wave activity (delta) throughout the brain and a left sided increase in fast (beta) activity. The peak frequency is slowed in schizophrenia and this slowing is related to increased cerebral ventricular size.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02390-01 CBDB

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

An Exploration of Parietal Functions in Schizophrenia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Principal Investigator: Michael Myslobodsky, M.D., Clinical Brain Disorders Branch, NIMH

Others: Terry Goldberg, Ph.D., Clinical Brain Disorders Branch, NIMH, Daniel R. Weinberger, M.D., Chief, Clinical Brain Disorders Branch, NIMH

COOPERATING UNITS *(if any)*

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Clinical Brain Disorders Branch

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Section on Clinical Studies

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| .1 | 3 | 0 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

We have found that schizophrenic patients show imitative dyspraxia of manual sequences and have difficulty in imitating facial sequences. Also, they are less competent than controls matched for sex, age, and education in lipreading of lexcal items overlearned sentences, but not words and syllables. These findings implicate the parietal lobe. Since the neuropsychology of schizophrenia is commonly conceived as akin to the "frontal lobe syndrome" these findings call attention to the possibility that the involvement of the parietal area in schizophrenia may be greater than formerly thought.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02391-02 CBDB

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Clinical Phenomena in Schizophrenia and the Development of Novel Treatments

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Principal Investigator: Craig N. Karson, M.D., Staff Psychiatrist, Clinical Brain Disorders Branch, IRP, NIMH

Others: David G. Daniel, M.D., Medical Staff Fellow, Clinical Brain Disorders Branch, IRP, NIMH, Llewellyn B. Bigelow, M.D., Clinical Director, WAW Division, Saint Elizabeths Hospital, IRP, NIMH; Darrell G. Kirch, M.D., Associate Clinical Director, NPB, IRP, NIMH; Joel E. Kleinman, M.D., Ph.D., Deputy Chief, Clinical Brain Disorders Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

Neuropsychiatry Branch, NIMH

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Clinical Brain Disorders Branch

SECTION

Section on Clinical Studies

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| .6 | .5 | 0 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Despite wide variations in the clinical manifestations of schizophrenia, it remains difficult for clinicians to design novel treatments or predict vulnerability to negative outcomes (including medication side effects) based on signs and symptoms of the disorder. By focusing on certain clinical characteristics of schizophrenia, we have designed a series of experimental medication treatments. This involves the notion that the disorder is associated with impairment cognitive performance. Hence, we have begun trials of medication that may improve cognition. Our first such trial utilized DDAVP with at least modest success. We are in the process of completing a trial of hydergine, another medication associated with improved cognition.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

## NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 MH 02392-01 CBDB

PERIOD COVERED
October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Evaluation Of Patients With Prefrontal Leukotomies

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Karen Faith Berman, M.D., Staff Psychiatrist, Clinical Brain Disorders Branch, IRP, NIMH; Barbara P. Illowsky, M.D., Medical Staff Fellow, Clinical Brain Disorders Branch IRP, NIMH; Daniel R. Weinberger, M.D., Chief, Clinical brain Bisorders Branch

Denise Juliano, MSW,Social Worker, Clinical Services Branch, WAW Division
Richard Suddath, M.D., Medical Staff Fellow, NPB,DIRP,NIMH; Terry E. Goldberg, Ph.D., Special Expert, CBDB,IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH
Clinical Brain Disorders Branch

SECTION
Section On Neuropathology Studies

INSTITUTE AND LOCATION
NIMH,WAW Bldg., St. Elizabeths Hospital

| | | |
|---|---|---|
| TOTAL MAN-YEARS:<br>10 | PROFESSIONAL:<br>6 | OTHER:<br>2 |

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Prefrontal lobotomies for psychiatric illness were last performed in the 1950's. Approximately 40 patients who had dorsolateral prefrontal lobotomies remain on the patient rolls at St. Elizabeths Hospital. The long-term effects of prefrontal lobotomy and the overall outcome of the patients is not clearly known. Techniques are now available to study anatomic, clinical and physiological aspects of lobotomy patients. These include computerized tomography scanning (CT), magnetic resonance imaging (MRI), and cerebral blood flow (cbf) examination. Neurological, psychiatric, and psychological evaluation of these patients in correlation with the above examinations compared to age and diagnosis matched-non-lobotomized patients, will give information on both the effects of prefrontal lobotomy and on the function of prefrontal cortex.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02393-01 CBDB

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Demeclocycine In The Treatment Of Psychogenic Polydipsia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Barbara P. Illowsky, M.D., Medical Staff Fellow, Clinical Brain Disorders Branch, NIMH

George Christison, M.D., Staff Fellow, Clinical Brain Disorders Branch, NIMH;
Darrell G. Kirch, M.D., Senior Staff Fellow, NPB,DIRP,NIMH;

COOPERATING UNITS *(if any)*

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Clinical Brain Disorders Branch

SECTION

Section On Neuropathology Studies

INSTITUTE AND LOCATION

NIMH,WAW Bldg., St Elizabeths Hospital

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 5 | 3 | 1 |

CHECK APPROPRIATE BOX(ES)

☑ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
 ☐ (a1) Minors
 ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Patients with psychogenic polydipsia (compulsive water drinking) comprise about 6% of the schizophrenic population. These patients are usually managed by imposed fluid restriction with symptomatic treatment for episodic water intoxication. Many of these patients have been shown to have inappropriate secretion of antidiuretic hormone (SIADH) which may be a factor in their episodes of hyponatremia.

Demeclocycline is an antibiotic related to tetracycline which blocks the action of antidiuretic hormone (ADH) and is useful in treating SIADH of diverse etiologies. Preliminary study has suggested that demeclocycline might be useful in psychiatric patients with psychogenic polydipsia.

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 MH 02394-02 CBDB

PERIOD COVERED
October 1, 1987 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Magnetic Resonance Imaging (MRI) Studies

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*
Daniel R. Weinberger, M.D., Chief, Section on Clinical Clinical Brain studies, NPB,DIRP,NIMH

Dr. Richard Suddath, Medical Staff Fellow, Clinical Brain Disorders Branch DIRP,NIMH: Dr. John Kelsoe, Medical Staff Fellow, Clinical Neuroscience Branch, NIMH; Dr. David Pickar, Chief, Section on Clinical Studies, CNB, IRP, NIMH; Dr. Manual Casanova, CBDB, Dr. George Christison, Dr. Terry Goldberg, Dr. Fuller Torrey

COOPERATING UNITS *(if any)*
Clinical Neuroscience Branch, NIMH; Section On Clinical Studies, CNB

LAB/BRANCH
Clinical Brain Disorders Branch

SECTION
Section On Clinical Studies

INSTITUTE AND LOCATION
NIMH, WAW Bldg., St. Elizabeths Hospital

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 3 | 1 | 1 |

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

We are studying the neuroanatomical localization of the possible underlying pathology using MRI. Attempts will be made to correlated neuroanatomical abnormalities to other findings such as those seen in blood flow or BEAM studies. These studies are using state of the arts digitized image analysis system to examine gray-white matter quantitative differences between schizophrenic and normals. Preliminary results indicate that patients have larger ventricles and less temporal gray matter. This represents potentially important evidence of a relatively focal pathological process.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02395-02 CBDB

PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Structural Brain Imaging In Schizophrenic Patients And Normal Subjects

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Daniel R. Weinberger, .D., Chief, Clinical Brain Disorders Branch, NPB,IRP, NIMH
David G, Daniel, CBDB; Dr. George Jaskiw, Visiting Associate, Section on Clinical Brain Studies, NPB, IRP, NIH; Dr. Barbara Illowsky, Medical Staff Fellow, Section on Clinical Brain Studies, NPB, IRP, NIMH;

COOPERATING UNITS *(if any)*

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Clinical Brain Disorders Branch

SECTION

Section On Clinical Studies

INSTITUTE AND LOCATION

NIMH, WAW Bldg., Saint Elizabeths Hospital

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 2 | 1 | 0 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The project on structural brain imaging investigates structural pathology of the brains of schizophrenic patients housed in the William A. White research units using x-ray computerized tomography (CT). Patients are compared to matched normal controls. The most recent study, a culmination of four years of data collection, compared 73 schizophrenic patients to 30 normal volunteer controls. This project is a replication and extension of the previous work done in this area in the branch. Using standardized techniques four brain areas were examined: Lateral ventricles, third ventricles, cortical (parieto-occipital) areas, and prefrontal cortex. In this sample, the lateral and third ventricles continued to be significantly larger in patients than controls. A potentially exciting new finding was that though there were essentially no differences between patients and controls in cortical atrophy in the parieto occipital distribution, the schizophrenic patients showed substantially greater atrophy in the prefrontal distribution, localizing the cortical changes to this area. Further, in a subgroup of 18 drug-free and 22 medicated patients, the CT abnormalities were correlated with regional cerebral blood flow (rCBF) using the radioactive 133 Xenon inhalation technique. Relationships were found between the neurophysiological measurements and CT scanning, especially in the prefrontal cortex and ventricular areas. This work is being amplified to search for clinical and biological correlations of ventricular enlargement and prefrontal atrophy, particularly with respect to other signs of prefrontal pathology, e.g. rCBF, EEG, PET data. In addition, we followed up earlier patients, rescanning them after 9-9 years. We have found no change over time, indicating that the pathology underlying these changes is probably static.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02397-02 CBDB

PERIOD COVERED

October 1 1986 through September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Hierarchy and Sensitivity in Putative Frontal Lobe Tasks

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Dr. Terry Goldberg, Special Expert, Clinical Brain Disorders Branch, IRP,NIMH

Dr. Daniel weinberger, Chief Clinical brain Disorders Branch, NPB, IRP, NIMH;
Dr. John Kelso, Section on Clinical Studies, Clinical Neuroscience Branch, NIMH

COOPERATING UNITS *(if any)*

Section on Clinical Studies, Clinical Neuroscience Branch, NIMH

LAB/BRANCH

Clinical Brain Disorders Branch

SECTION

Section On Clinical Studies

INSTITUTE AND LOCATION

NIMH, WAW Bldg., Saint Elizabeths Hospital, Washington, D.C.

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
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| .33 | .33 | 0 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Various standardized neuropsychological tests are thought to tap frontal lobe funtion to varying degrees. These involve verbal fluency, multiple tracking, category formation, and hypothetico-deductive reasoning and set shifting. The differential performance of schizophrenic patients with physiological frontal lobe dysfunctions of these tasks is unkown. We are investigating the sensitivity of the tests and the possibility that there is a hierarchical arrangement of them.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02398-01 CBDB

PERIOD COVERED

October 1, 1987 through September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Development of an Auditory Sort Test

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

Dr. Terry Goldberg, Special Expert, Clinical Brain Disorders Branch, IRP,NIMH

Dr. Daniel weinberger, Chief Clinical Brain Disorders Branch, Chief, Clinical brain Disorders Branch, NPB, IRP, NIMH; Dr. Craig Karson, Staff Staff Psychiatrist, NPB, IRP, NIMH; Dr. Karen F. Berman, Staff Psychiatrist, NPB, IRP, NIMH

COOPERATING UNITS (if any)

LAB/BRANCH

Clinical Brain Disorders Branch

SECTION

Section On Clinical Studies

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

| | | |
|---|---|---|
| TOTAL MAN-YEARS: .33 | PROFESSIONAL: .33 | OTHER: 0 |

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☒ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Concepts formation tasks with a set shifting component have proven sensitive to frontal lobe dysfunction. The Wisconsin Card Sort, perhaps the most widely known test of this class, activates prefontal regions in most normal but no schizophrenic subjects. It is presented in the visual modality. To futher validate the use of such a test and to facilitate cognitive activation in EEG-BEAM studies while reducing eye movement, an auditory analog of the card sort was developed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02399-02 CBDB

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Postmortem Brain Tissue Examination in Neuropsychiatric Disorders

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Joel E. Kleinman, M.D., Ph.D., Deputy Chief, CBDB, IRP, NIMH

Emanuel Casanova, M.D., Neuropathologist, CBDB; Daniel R. Weinberger M.D.,Chief, CBDB, Craig N. Karson, M.D., Staff Psychiatrist, CBDB, George Jaskiw, M.D., Staff Psychiatrist, Natanel Zelnik, M.D., Guest Worker, CBDB, Steven Paul,M.D., Chief, Clinical Neuroscience Branch, Farouk Karoum, Ph.D., Chemist, NPB, IRP, NIMH and Markku Linnoila, M.D.,Ph.D., Chief, NIAAA, NIMH;

COOPERATING UNITS *(if any)*

NIAAA; Neuroscience Branch, NIMH; Neuropsychiatry Branch

LAB/BRANCH

Clinical Brain Disorders Branch

SECTION

Section On Neuropathology Studies

INSTITUTE AND LOCATION

NIMH, WAW Bldg., St Elizabeths Hospital

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
|---|---|---|
| 5 | 2 | 3 |

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Postmortem Studies in neuropsychiatric disorders test hypotheses with regard to schizophrenia, suicide, Parkinson's Disease, addictions and aging. New findings include the following: Decreased numbers of D-1 dopamine receptors with increased affinity in schizophrenic patients in the caudate nucleus as compared with controls; (2) No evidence for transmission of viruses from schizophrenic brain specimens to controls; (3) Little evidence for lateralization of neuropeptides (somatostatin, and vasopressin, oxytocin) in schizophrenic brain samples and; (4) decreased dopamine reuptake binding in Parkinson's patients versus controls.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 MH 02400-01 CBDB

PERIOD COVERED
October 1, 1986 throught September 30, 1987

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Eight Year Follow-up Of Ventricular Size In Schizophrenia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Barbara P. Illowsky, M.D., Medical Staff Fellow, Clinical Brain Disorders Branch, NPB, IRP, NIMH

Denise M. Juliano, MSW, Social Worker, Clinical Services Branch, WAW Division; Dr. Llewellyn B. Bigelow, Associate Clinical Director, WAW Division, Saint Elizabeths Hospital, NIMH; Daniel R. Weinberger, M.D., Chief, Clinical Brain Disorders Branch, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH
Clinical Brain Disorders Branch

SECTION
Section On Neuropathology Studies

INSTITUTE AND LOCATION
NIMH, WAW Bldg., St. Elizabeths Hospital

| TOTAL MAN-YEARS: | PROFESSIONAL: | OTHER: |
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CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Cranial computerized axial tomography (CT) has been useful in identifying a subgroup of schizophrenic patients with enlargement of the lateral ventricles and frontal cortical atrophy. The relationship between these anatomic abnormalities and mental illness remains speculative, but it has been suggested that such enlargement may be more common in those patients with more severe illness or poor prognosis. Previous CT studies have shown no correlation between ventricular size and duration of illness or age and a single prospective study failed to show progressive ventricular enlargement over a brief, 3 year, follow-up period.

We rescanned a cohort of schizophrenic patients 7-9 years after a pilot study of ventricular size. This study greatly extends the follow-up period. No pattern of change in ventricular size or frontal cortical atrophy was seen, indicating that the pathology underlying these changes appears to remain static.

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